GASTROPARESIS IN GASTRO ESOPHAGEAL REFLUX DISEASE - PREVALENCE AND ASSESSMENT USING GASTRIC SCINTIGRAPHY WITH SYMPTOMATIC CORRELATION

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CHENNAI - 600 032

"learn to heal"

CERTIFICATE

This is to certify that the dissertation entitled **"GASTROPARESIS IN GASTRO ESOPHAGEAL REFLUX DISEASE – PREVALENCE AND ASSESSMENT USING GASTRIC SCINTIGRAPHY WITH SYMPTOMATIC CORRELATION"** is a bonafide original work of **DR. ARVIND M A** in partial fulfillment of the requirements for **D.M. Branch-IV (MEDICAL GASTROENTEROLOGY)** examination of **The Tamilnadu Dr.M.G.R. Medical University** to be held in August 2013. The period of Post-Graduate study and training was from August 2010 to July 2013.

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DECLARATION

I, **Dr. ARVIND, M.A.** solemnly declare that this dissertation entitled,"**GASTROPARESIS IN GASTRO ESOPHAGEAL REFLUX DISEASE-PREVALENCE AND ASSESSMENT USING GASTRIC SCINTIGRAPHY WITH SYMPTOMATIC CORRELATION** " is a bonafide work done by me at the department of Medical gastroenterology, Madras Medical College and Government General Hospital during the period 2010 - 2013 under the guidance and supervision of the Professor and Head of the department of Medical Gastroenterology of Madras Medical College and Government General Hospital, **Prof.MOHAMMED ALI, M.D.D.M.** This dissertation is submitted to The Tamil Nadu Dr.M.G.R Medical University, towards partial fulfillment of requirement for the award of D.M. Degree (Branch-IV) in Medical Gastroenterology.

Place : Chennai (**ARVIND M.A)**
Date :

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CONTENTS

INTRODUCTION

Gastroesophageal Reflux disease (GERD) is a condition that arises from reflux of gastric contents into the esophagus through the lower esophageal sphincter causing symptoms and/or injury to esophageal or extraesophageal structures. While normal people may experience reflux symptoms once in a while, say for example after a heavy meal these are usually infrequent and do not interefere with patients quality of life nor do they cause significant esophageal injury. Pathological reflux occurs when the esophageal defense mechanisms including acid clearance and mucosal resistance are overwhelmed by the injurious refluxate such as acid, pepsin, bile, duodenal contents. Lower Esophageal Sphincter(LES) is the most important component of antireflux barrier and is a tonically contracted smooth muscle of length 3-4cm located at the gastroesophageal junction. Resting LES pressure varies between 10-30 mm Hg and its reserve is high since even a pressure of 5-10mmHg can prevent reflux. Resting tone of LES is a function of both myogenic and neurogenic components. Acetyl choline released from muscarinic system is the predominant neurotransmitter in maintaining resting LES tone. In addition the diaphragmatic contractions augment LES pressure during inspiration. LES is designed naturally to prevent

reflux while at the same time it provides air venting through belching mechanism by relaxing transiently, especially postprandially, called as TLOSRs-Transient Lower esophageal Sphincter Relaxations. But, this natural mechanism of belch which when severe and frequent causes pathological reflux. TLOSRs are the predominant cause of GERD in most cases of GERD while in 20% cases LES incompetence is the causative factor. According to the MONTREAL Definition[1], gastro esophageal reflux disease is a condition which develops when the reflux of gastric contents causes troublesome symptoms and/or complications. The characteristic symptoms of GERD include retrosternal burning sensation and regurgitation which is defined as perception of flow of refluxed gastric content into mouth or hypopharynx. GERD related disease manifestations are further classified as esophageal and extraesophageal syndromes.

Esophageal syndromes include syndromes which are typically not associated with esophageal injury such as typical reflux syndrome, reflux chest pain syndrome and syndromes associated with esophageal injury such as endoscopic esophagitis, esophageal strictures, barretts metaplasia, adenocarcinoma. extraesophageal syndromes with established associations include reflux cough syndrome, laryngitis, asthma, Dental erosions.

Diagnosis of GERD may be accompalished by different methods including symptomatic criteria, endoscopic criteria, Biopsy criteria, ambulatory pH Monitoring criteria. The typical reflux disease is symptomatically defined and it does not require diagnostic testing[2.] An empirical trial of acid suppression is the most definitive test to diagnose GERD and assess its relation to symptoms. Symptoms usually respond to trial of PPI in one to two weeks. Reflux esophagitis is the term used to encompass endoscopically demonstrable esophageal mucosal breaks, erosions and also normal endoscopic appearances but histological evidence of dilated intercellular channels usually demonstrable with electron microscopy[3] Absence of visible erosions is noted in over 50% of patients presenting. With typical reflux symptoms[4] Reflux esophagitis is diagnosed by endoscopy when visible breaks are noted in esophageal mucosa at or above gastroesophageal junction.Various classification systems have been published To assess severity of endoscopic esophagitis but the Los Angeles Classification System has gained general acceptance. [5] Ambulatory pH monitoring is a standard test to establish pathologic reflux and reflux episodes are defined by pH drop less than 4.

Not all cases of GERD present with typical symptoms and there exists a subset of cases who may present with additional symptoms of nausea, early satiety and postprandial fullness. This subset may

represent an overlap syndrome with functional dyspepsia and account for 30% of GERD cases which is a significant proportion[6]. Gastric emptying of chyme is the most important mechanical function of stomach. Studies have demonstrated that a quarter of patients with GERD demonstrate delayed gastric emptying [7] Prior studies of gastric emptying assessment in GERD have included specific risk factors for gastroparesis such as diabetes mellitus and therefore have spuriously high prevalence of gastroparesis in GERD cases. Exclusion of specific risk factors of gastroparesis is therefore important to identify idiopathic gastroparesis in GERD cases.

The pathophysiological relationship between GERD and gastroparesis is multifactorial and bidirectional i.e one may affect another by multiple mechanisms. tLOSRs may contribute to delayed GE[8]. GERD patents also tend to retain solids in proximal stomach more than controls and this may stimulate additional tLOSRs[9]. Gastric emptying can be assessed by number of methods including scintigraphy, MRI, functional USG. Tests such as MRI are evolving and it does not provide direct assessment of meal emptying since the volume of gastric contents has to be corrected for gastric secretions which dilute the meal[10] Functional ultrasonography is best suited for assessment of liquid phase emptying which is of limited clinical utility since it does not become abnormal till gastroparesis is severe[11].

Gastric scintigraphy with solid phase labeling is considered to be the gold standard test for assessment of gastric emptying since it provides visual assessment of gastric emptying and has been used in number of studies. Scintigraphy not only provides global GE values but also assesses retention of food in antrum versus fundus, thus providing regional GE values which may help understand pathophysiological correlation between gastroparesis and propensity for reflux. This is important to know since PPIs do not address gastric neuromuscular dysfunction. Thus it may help decide choice of treatment such as additional role for prokinetics, fundic relaxants such as acotiamide, surgical management any of which need to be considered since PPI alone may not control symptoms gastroparesis in this sub set of overlap cases. Objective measurement of gastric emptying can be coupled with symptom profile assessment after ingestion of test meal to find if any symptomatic correlation exists. This study titled "Gastroparesis in gastroesophageal reflux disease - prevalence and assessment using gastric scintigraphy with symptomatic correlation" is a prospective study conducted in the Department of Medical Gastroenterology, Rajiv Gandhi Government General Hospital, Madras Medical College and Advanced Nuclear Medicine Research Centre, Chennai.

AIM

To study the prevalence of gastroparesis in GERD patients and assessment of the same by gastric scintigraphy and correlate it with gastroparesis cardinal symptom index.

REVIEW OF LITERATURE

GERD AND FUNCTIONAL DYSPEPSIA

Gastroesophageal reflux disease and functional dyspepsia are two common upper gastrointestinal disorders encountered in clinical practice. GERD is defined by montreal definition as a condition which develops when reflux of gastric contents causes troublesome symptoms and /or complications. Heart burn and regurgitation represent two of characteristic symptom

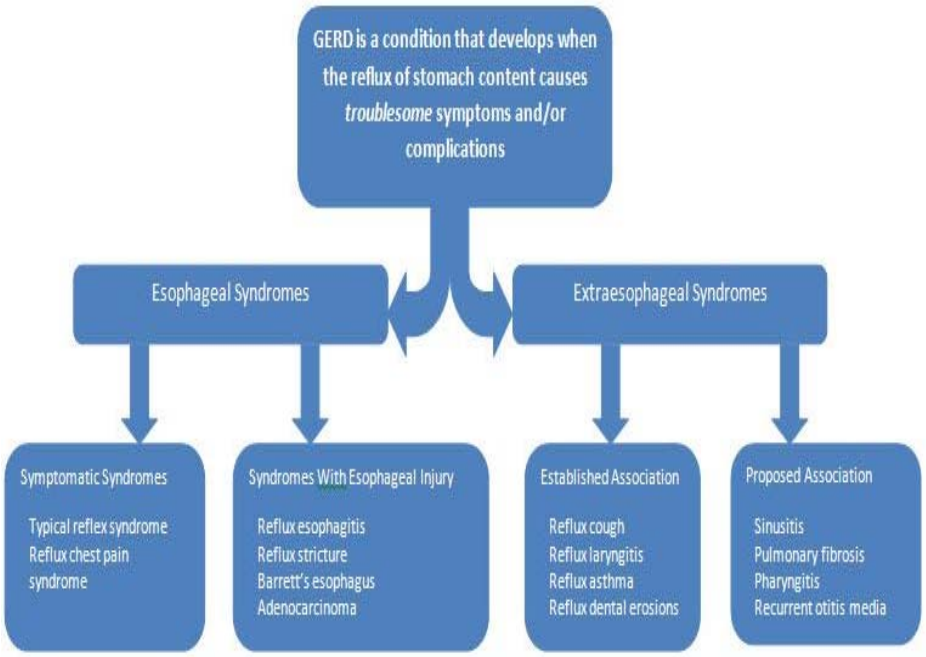


FIGURE 1: MONTREAL DEFINITION OF GERD[1]

Functional dyspepsia on the other hand is defined by Rome III criteria as presence of symptoms thought to originate in gastroduodenal region which include nausea/vomiting, postprandial fullness or early satiety, abdominal bloating. It also classifies FD into two distinct entities namely the epigastric pain syndrome and postprandial distress syndrome. Although GERD and FD appear distinct based on definitions, there is a significant overlap noted in epidemiology, pathophysiology, genetics, symptomatic presentation, diagnostic and therapeutic aspects of these two diseases.

EPIDEMIOLOGICAL OVERLAP - INDIAN SCENARIO

Traditionally GERD is thought to be a disease of western world where prevalence of 10-20% have been reported. In India prevalence rates were thought to be low (<5%) but recent studies which enrolled large number of cases in urban and rural populations have shown that prevalence rates of GERD varies between 7.6 percent[12] to 18.7 percent[13] indicating prevalence trends similar to the west. This could be attributed to socioeconomic development, adoption of western diet, epidemic of obesity and reduction in H pylori prevalence. World wide prevalence of FD is around 20-30%[14] whereas the minimal Indian literature on FD gives a prevalence range of 7.5 %[15] to 49%.[16] Thus we can see clearly

that there is significant epidemiological overlap of these two conditions in India.

PATHOPHYSIOLOGICAL OVERLAP

GERD has traditionally been classified as Erosive Reflux disease (ERD), Non erosive reflux disease (NERD) and complicated disease which includes barretts metaplasia, adenocarcinoma, strictures. NERD has been classified into 3 subtypes based on 24h ambulatory pH monitoring studies[17]

TABLE 1 : NERD SUBGROUPS

NERD subgroups	Type 1	Type 2 The "sensitive" esophagus	Type 3 Functional heartburn
Acid exposure time	Abnormal	Normal	Normal
Symptom–reflux correlation	Positive	Positive	Negative
Response to acid suppression	Yes	Yes	None

The likelihood of overlap between the two disorders is greater in patients with NERD than ERD. Even within the subtypes of NERD, overlap of FD is greatest among patients with functional heartburn[18] An overlap between GERD and FD would certainly be expected on the basis of interrelated physiology of lower esophageal sphincter and

gastric fundus. Gastric fundus is intimately involved in triggering tLOSRs which are fundamental to GERD.[19]

A study of overlap cases classified patients into 3 categories including GERD alone, FD alone, GERD with FD.[20] It assessed regional and global gastric emptying in each category. Gastric emptying was found to be delayed in 50% cases in each category. Fundal retention of food was noted in GERD cases and antral retention of food noted in overlap cohorts. Gastric dysmotility may explain relative ineffectiveness of PPI therapy in patients with overlap cases and also why prokinetics may help in such cases[21]

GENETIC OVERLAP

G protein Coupled Receptors are involved in signal transduction. Altered function of GPCRs are noted to be associated with depression in Functional dyspepsia cases, especially the GNB3 subunit polymorphism (C825 T). Three genotypes can arise out of this polymorphism including TT,CT, CC genotypes.CC genotype is associated with reduced levels of the beta 3 splice variant resulting in impaired GPCR signal transduction. This CC Genotype has been found to be associated with FD symptoms[22] The authors postulate that reduced intracellular signal transduction can result in dysregulation of antinociceptive pathway and

thus link it to abdominal pain in FD. Studies have also evaluated GPCR polymorphisms in GERD cases. The reason for evaluation being that GPCRs mediate response to acid and modulate esophageal sensory function.GERD has been shown to be associated with GNB3 C825 T Polymorphism.[23]

SYMPTOMATIC OVERLAP

Heart burn and regurgitation are the cardinal symptoms of GERD whereas epigastric discomfort which includes burning, pressure or fullness with or without abdominal bloating,early satiety characterize FD and symptoms may be postprandial. Thus epigastric burning discomfort may be misunderstood as retrosternal discomfort creating dilemma. Also symptoms of GERD and FD may coexist in true overlap cases.

DIAGNOSTIC TESTING-OVERLAP

24h pH monitoring

A prospective study of 247 FD patients showed that 23 % of cases had abnormal 24 h pH study defined by acid exposure more than 5% of time. Interestingly these patients did not report GERD Symptoms[24] This study highlights diagnostic overlap of FD with GERD. Gastric

emptying studies Gastric emptying is delayed in 30% of cases of FD[25] Delayed gastric emptying especially of proximal stomach may promote reflux of gastric contents resulting in GERD, thus creating a scenario for overlap. Thus gold standard tests for diagnosis of GERD and FD, namely 24h pH study and gastric emptying studies may not be clearly delineate specific disorders due to propensity for overlap noted between these two conditions.

THERAPEUTIC OVERLAP

PPI (Proton Pump Inhibitor)

Both GERD and FD are currently managed with PPIs. While PPIs are considered the standard of care in GERD, several studies have shown that PPIs have either no benefit[26] or only modest benefit[27] in patients with FD.A metaanalysis of 7 randomized control trials of PPI in FD patients (n=3725) showed a significant benefit with PPI use compared to placebo.[28] In general it is agreed that FD patients with reflux related symptoms benefit from PPI therapy than those without it.

PROKINETICS

Theoretically, prokinetics seem a good choice for management of GERD since these drugs act by increasing resting LES Pressure and

by accelerating gastric emptying. This effect is illustrated by cisapride (mixed 5HT4 Agonist and 5HT3 Antagonist) ,the best studied prokinetic agent in GERD. However the potential to cause QT prolongation and cardiac arrhythmias led to its withdrawal from market. Prokinetics in general have limited role in management of GERD due in part to the side effect profile of the drugs available.

A variety of prokinetics have been tried in FD cases. Tegaserod, the first agent tried showed only marginal benefit in FD cases[29] but cardiac side effects limit its use.Phase III trials of itopride did not show any benefit over placebo in FD cases[30]

FUNCTIONAL ORGANIZATION OF GASTRIC MOTILITY

OVERVIEW

The Stomach is a hollow organ functionally separable as proximal and distal portions, with presence of sphincters at both ends.[31] This arrangement reminds one of cardiac chambers especially the cardiac valves and the ventricles proper which have an inlet portion to receive blood from the atria and an outflow portion which pumps blood into the great vessels, to allow oxygenation and delivery of blood to every tissue in our body. Also, both the organs have a pacemaker indicating how gastric emptying and cardiac ejection are

functionally similar. Proximal portion of stomach is functionally distinct from distal portion and this separation allows for efficient functioning of stomach.

COMPONENTS OF GASTRIC MOTILITY

GASTRIC PACEMAKER AND ORIGIN OF SLOW WAVES

At the cellular level , the most important structure is the smooth muscle cell with the ICC-Interstitial cells of Cajal being specialized form. The characteristics of smooth muscle cells of proximal stomach vary from those located in distal stomach. Proximal stomach smooth muscle cells generate tonic contractile activity whereas distal stomach smooth muscle Cells generate phasic contractile activity. The rhythmic electrical activity Responsible for phasic contractions of antrum is called as Slow waves.

The Slow waves have their origin from interstitial cells of Cajal, located In the gastric pacemaker in the greater curvature in region of corpus. Slow Waves are nothing but oscillations in membrane potential occurring at Rate of 3 cycles per minute(cpm) with action potential peaks in between determining both the frequency and strength of gastric contractions.

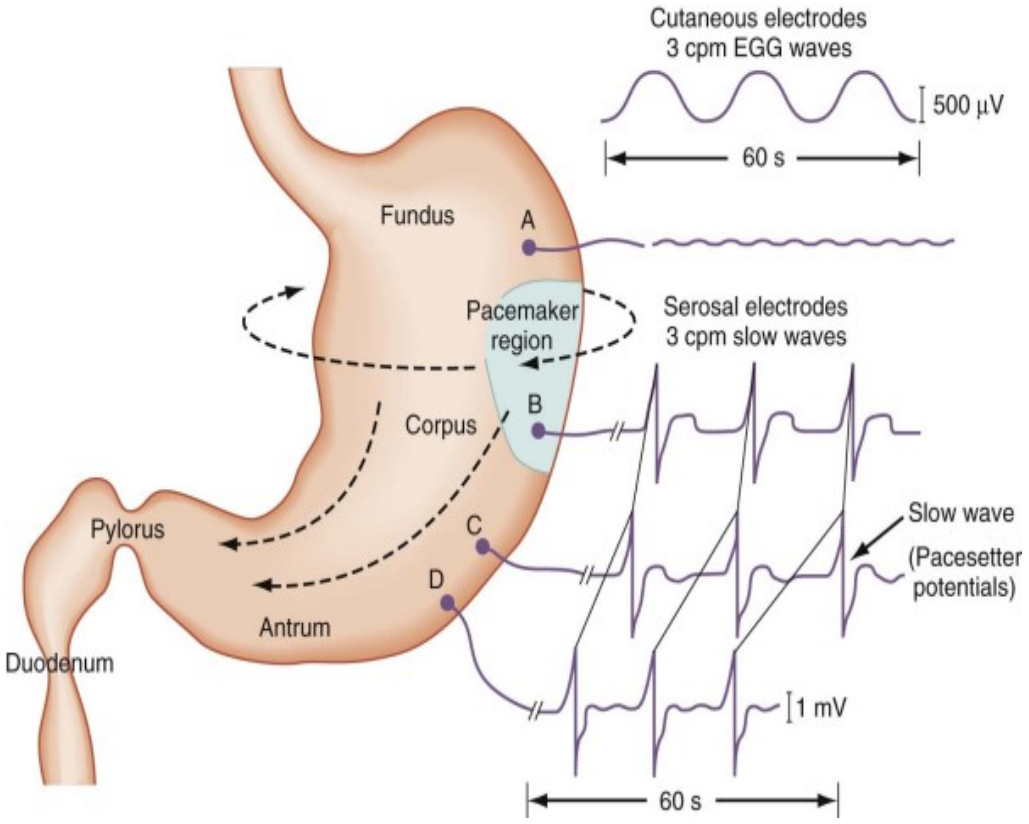


FIGURE 2: GASTRIC ELECTRICAL ACTIVITY

MYENTERIC PLEXUS

Gastric wall comprises the inner circular and outer longitudinal muscle layers, with the myenteric plexus sandwiched in between. This plexus, although receiving inputs from extrinsic nervous system, including vagus and sympathetics, is characterized by its functional autonomy.

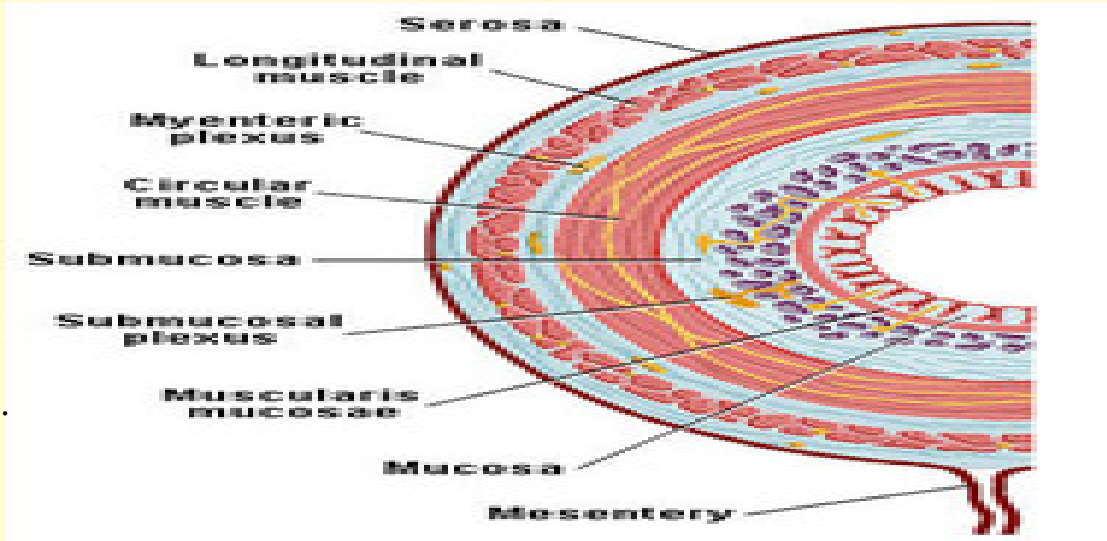


FIGURE 3: MYENTERIC PLEXUS

EXTRINSIC INNERVATION OF STOMACH

PARASYMPATHETIC SUPPLY

Derived from vagus.90% of innervation is sensory and only 10% Is motor. The Sensory innervation is carried via nucleus tractus solitarius to the brainstem and the vagal efferents originate from dorsal motor nucleus to complete this vagovagal pathway which has important role in regulating gastric motility.

SYMPATHETIC SUPPLY

Derived from spinal segments T6-T9. This system acts as negative regulator of motility of stomach via inhibition of presynaptic release of acetylcholine from myenteric plexus.

FASTING STATE VERSUS FED STATE GASTRIC ACTIVITY

IS STOMACH QUIESCENT IN FASTING STATE?

In fasting state,stomach and small intestine demonstrate cyclical motor activity called as Migrating Motor Complex (MMC) which has three specific phases spread over 90-120 min.

Phase I

Consists of no demonstrable contractile activity.

Phase II

Consists of irregular contractions.

Phase III

Consists of regular contractions.

Phase III of MMC occurs at a rate of 3 cpm in stomach and 12 cpm In duodenum. It migrates along length of gut at rate of 1-4cm

per minute. Phase III of MMC is responsible for clearance of indigestible food residue from stomach and proximal intestine.

FED STATE

GASTRIC HANDLING OF SOLID MEAL

PROXIMAL STOMACH –RESERVOIR FUNCTION

In the fasting state, gastric fundus exhibits tonic contraction called as fundic tone and is mediated by vagovagal pathway. But, as the food descends from esophagus into proximal stomach, two temporally spaced events occur.

1. Receptive relaxation
2. Adaptive relaxation

Receptive relaxation occurs immediately after food intake when gastric fundus relaxes to increase gastric volume whereas adaptive relaxation occurs awhile later and is characterized by sustained relaxation of proximal stomach.

DISTAL STOMACH-THE PUMP

Fundus of stomach contracts and pushes the food into corpus and antrum. Here, milling or trituration begins whereby food is grinded

into smaller particles of size 1-2mm, the chyme. The period from intake till gastric emptying into duodenum is called the lag phase. Then, linear phase of gastric emptying begins when peristalsis occurs every 20 seconds and empties 3-4ml of chyme.

RESISTANCE TO GASTRIC EMPTYING

Resistance to gastric emptying of chyme into duodenum is provided by pylorus which modulates resistance as a function of diameter change and also by duodenum. This allows delivery of nutrients from stomach to duodenum at a rate which is ideal for nutrient absorption. This mechanism is called as antropyloroduodenal coordination.

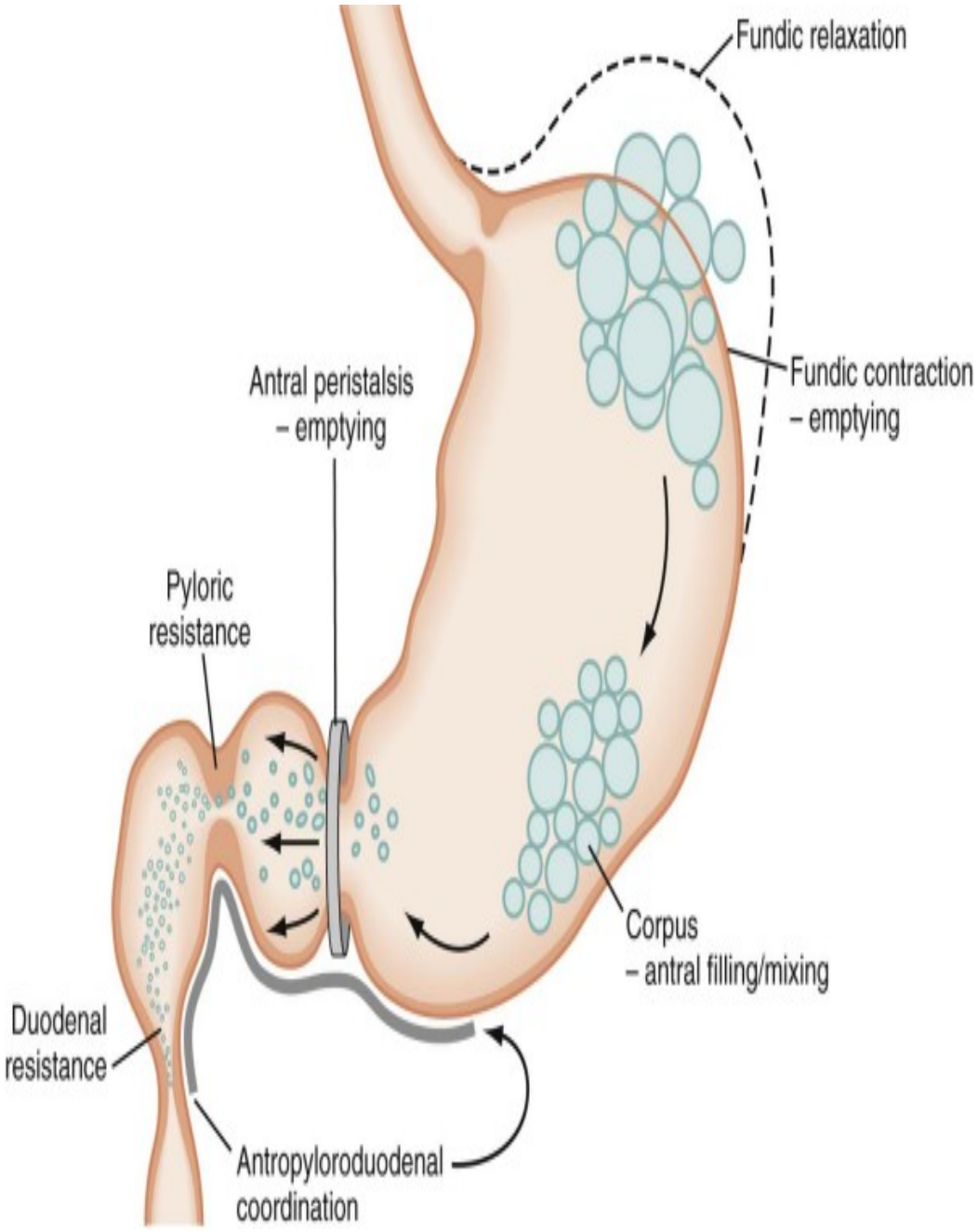


FIGURE4: SPECTRUM OF WORK IN GASTRIC EMPTYING OF SOLID MEAL

GASTRIC EMPTYING OF LIQUID MEAL

Significant differences exist between gastric emptying of liquid meal in contrast to solid meal, and include

1. Fundus, body, antrum relax nearly simultaneously to accommodate larger quantities of liquid.
2. Emptying occurs at a rapid rate than solids.
3. Non caloric liquids empty without lag phase.

TESTS IN ASSESSMENT OF GASTRIC EMPTYING INCLUDING SCINTIGRAPHY

Gastric emptying of chyme is the most important mechanical function of the stomach. It has fascinated researchers similar to cardiac ejection of blood.The history of assessment of gastric emptying is as fascinating as the process itself. Direct observation of gastric contents across a fistula.[32] aspiration methods to study gastric contents, use of pH devices, isotope breath tests have all been tried in the past to evaluate gastric emptying. But,the modality that attracted most attention has been imaging methods which allows direct visualization of passage of gastric contents from the stomach into the intestines. Walter B Cannon was a pioneer in this regard, his animal studies

involved administration of radioopaque contrast and use of fluoroscopic imaging to visualize gastric emptying of the contrast.[33] This was not a practical method that can be applied in humans since it involved considerable radiation exposure.

Barium pellets incorporated into solid meal and use of serial abdominal xrays to analyze gastric transit have also been tried, but the size and nature of the pellets allows it to be emptied only during return of inter-digestive migrating motor complex and not during emptying of chyme.[34] In recent times, gastric scintigraphy has emerged as the most widely used imaging modality in the assessment of gastric emptying. It was introduced in 1966, in a pioneering work by a group of investigators [35] who used chromium 51 as a radiolabel to assess gastric emptying of meal. This study had potential error due to early label decay and adherence of label to stomach lining long after food passed into intestines.

Then a specific solid label was developed in 1976 when 99m technetium was injected into live chickens, getting incorporated into liver. After slaughter liver was cooked and used as solid phase label.[36] Solid phase labeling became simpler when 99m technetium was incorporated into the colloid matrix of scrambled eggs [37]

Initial studies used both solid phase and liquid phase labeling using dual isotopes to study emptying of each. But, it became clear with further studies that liquid phase emptying is grossly different from solid phase emptying in that liquids do not require trituration unlike solids and also that liquid phase emptying becomes abnormal only when gastroparesis is severe. Thus, solid phase emptying alone came to be studied in subsequent studies with use of single label.After radiolabeling the solid meal, the gastric counts measured by scintigraphy correlate directly with the volume of meal retained in stomach without the need for geometric assumptions about shape of stomach.

FACTORS TO BE CONSIDERED IN MEASUREMENT OF GASTRIC EMPTYING PATIENT RELATED FACTORS

The three important patient related factors to be considered in measurement of GE include medications, tobacco smoking, hyperglycemia. Medications that affect gastric motility such as prokinetics or opioids need to discontinue drug therapy for atleast 48-72 hours prior to test. Tobacco smoking has been shown to delay gastric emptying in prior studies[38] It has been recommended that patients refrain from smoking on the morning of the test and also during the performance of test. Hyperglycemia[39] can delay gastric

emptying and therefore patient serum glucose level must be controlled to values of 180-275mg/dL prior to test, this being achieved with use of Insulin on the day of study.

TECHNICAL FACTORS

(A) OPTIMAL MEAL

Meals currently used for gastric emptying studies include chicken liver, eggs, oatmeals, pancakes. The content of meal is the most important factor that requires standardization and guidelines[40] recommend low fat, egg based meal as the reference standard. The technetium 99m –sulfur colloid egg meal consists of equivalent of two large eggs, two slices of bread (120Kcal) and strawberry jam (30g,74 Kcal), water (120ml) ,0.5-1mci of Tc99m - sulfur colloid. technetium has affinity for the protein matrix of egg white and gives good quality images.

(B) IMAGE ACQUSITION

The radiolabeled meal must be ingested quickly within 10 min. Images have to be obtained in 64 x 64 pixel format using a general purpose collimator. A 128x128 word mode image matrix is used. The photopeak settings are 20% at the 140ke V peak of technetium 99m. Anterior and posterior planar images with distal esophagus, stomach

and proximal small intestine in the field of view must be obtained for a period of 1 min after meal ingestion.

FIGURE5 : IMAGE OF GE MILLENIUM MPR SPECT GAMMA CAMERA

(C) OPTIMAL IMAGING TIMES

A multinational study established the optimal imaging points, normal values for gastric emptying [41] The study enrolled 123 normal subjects from 11 medical institutions in USA, Canada, Europe and imaging was done at 0,1,2,4 hours after ingestion of radiolabeled meal. This study established the normal control values for gastric emptying time as ULN-upperlimits of normal(95^{th} percentile).Delayed gastric emptying was defined as >90% retention at 1 hour, > 60% retention at 2 hours, >10% retention at 4 hours. This study is by far the largest published database of standardized gastric emptying protocol. Imaging

at 4 hours after meal intake is critical since a patient with normal emptying at 2 hours , may show delayed emptying at 4 hours and vice versa.

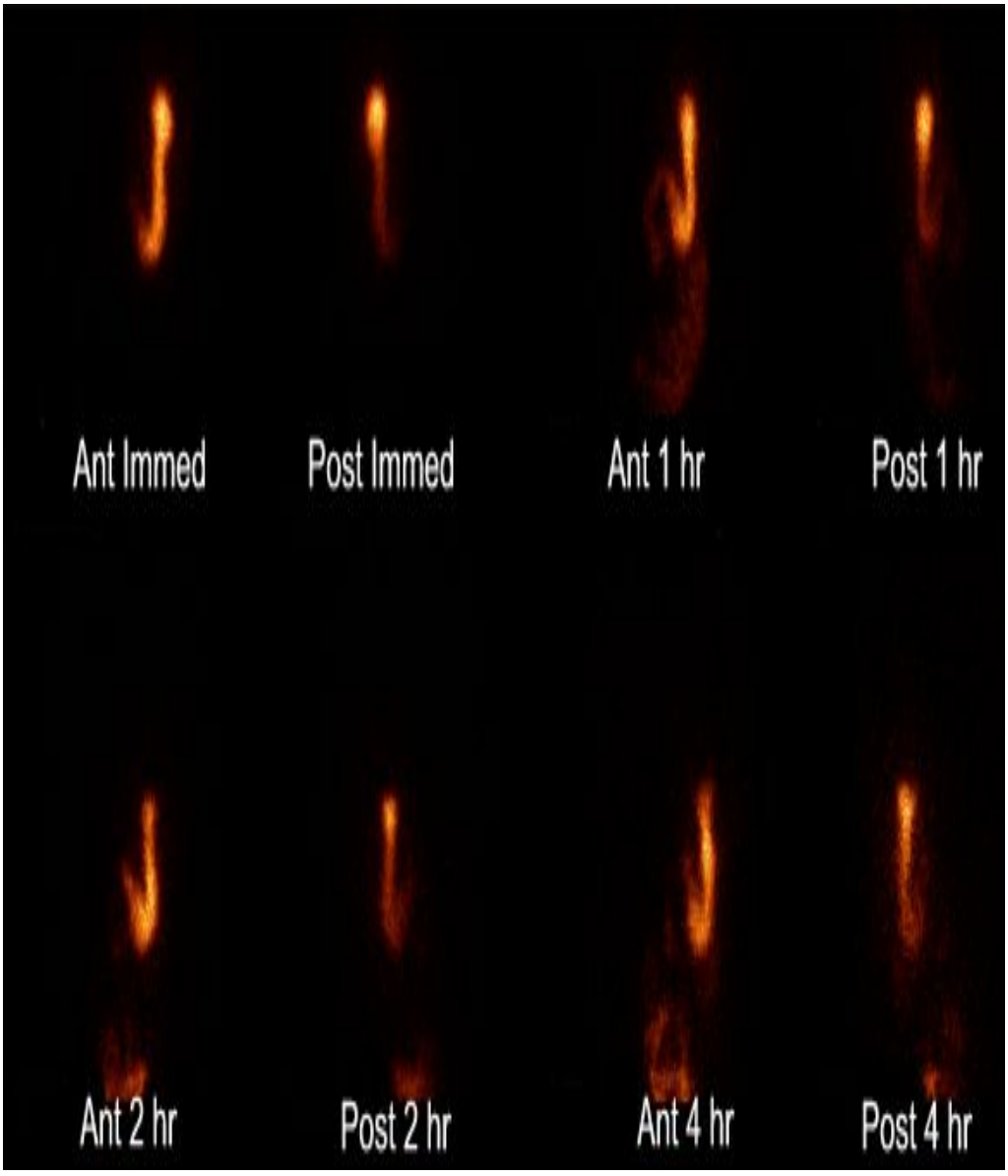


FIGURE 6 : OPTIMAL TIME POINTS IN IMAGING

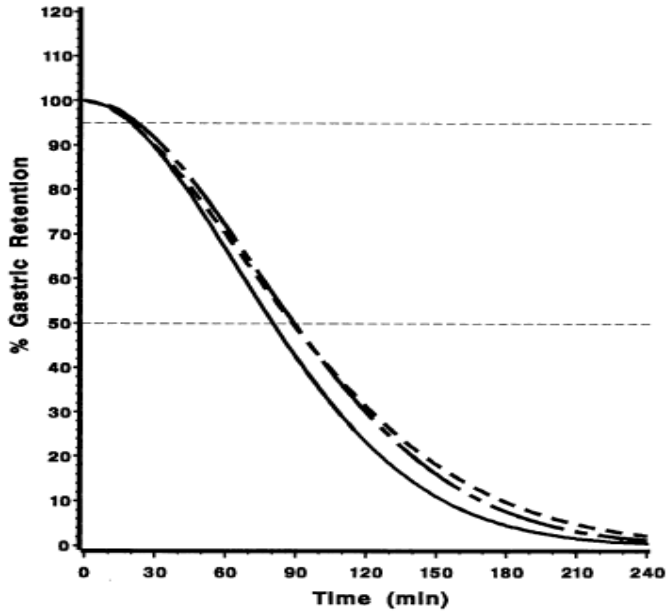


FIGURE 7 : SOLID PHASE GASTRIC EMPTYING CURVE IN NORMAL INDIVIDUALS

(D) IMAGE ANALYSIS TO QUANTIFY GASTRIC EMPTYING

Irregular ROI-Region of interest tool is used to draw an outline of stomach .Manual ROI are drawn on the anterior and posterior images. The total gastric ROI must include fundus and antrum, with attention to avoid small intestinal loops. The geometric mean(GM) of anterior and posterior gastric counts is calculated at each time point and may be corrected for decay of 99m Tc. GM=(Anterior counts x

Posterior counts)$^{1/2}$. The final result is expressed as percent remaining in stomach at each time point .

(E) ASSESSMENT OF REGIONAL GASTRIC EMPTYING: FUNDUS VERSUS ANTRAL RETENTION

Regional gastric emptying analysis is helpful in understanding pathophysiology related to dyspeptic symptoms. Fundal versus antral retention of food can be assessed by gastric scintigraphy by applying irregular ROI tool. Fundal retention of food has been associated with early satiety whereas antral retention of food has been associated with vomiting .

(F) GRADING OF GASTROPARESIS[40]

TABLE 2

GASTROPARESIS GRADE	PERCENT RETENTION AT 4HOUR
MILD	11-20
MODERATE	21-35
SEVERE	36-50
VERY SEVERE	>50

(G) SYMPTOM ANALYSIS DURING PERFORMANCE OF GASTRIC EMPTYING TEST

Monitoring of symptoms of gastroparesis after ingestion of radiolabeled meal may help to correlate clinical symptoms with objective assessment of delayed gastric emptying. Symptoms of gastroparesis may be quantified by a validated questionnaire ,the GCSI-gastroparesis cardinal symptom index. It is based on three scales namely early satiety, abdominal bloating,vomiting.[42] The Total Score of GCSI ranged from 0-5 and it takes into account the total of 9 subscales derived from aforesaid 3 scales.

TABLE 3: GASTROPARESIS CARDINAL SYMPTOM INDEX SUBSCALES

		None	Very mild	Mild	Moderate	Severe	Very severe
1.	Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2.	Retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3.	Vomiting	0	1	2	3	4	5
4.	Stomach fullness	0	1	2	3	4	5
5.	Not able to finish a normal-sized meal	0	1	2	3	4	5
6.	Feeling excessively full after meals	0	1	2	3	4	5
7.	Loss of appetite	0	1	2	3	4	5
8.	Bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9.	Stomach or belly visibly larger	0	1	2	3	4	5

MATERIALS AND METHODS

The study was conducted at Department of Medical Gastroenterology Rajiv Gandhi Government General Hospital-Chennai and Advanced Nuclear Medicine Research Institute-Chennai from Feb 2012 to Feb 2013 .In all patients history was taken and physical examination done. Then they underwent baseline investigations including complete blood count, fasting and post prandial blood sugar, renal function test, ultrasound abdomen, upper gastrointestinal endoscopy with grading of esophagitis when present, biopsy of lower esophagus was taken if showing severe esophagitis or suspicious for baretts esophagus. Two patients had already undergone 24h ambulatory pH monitoring as part of evaluation outside. GERD was diagnosed by symptomatic criteria – montreal definition(28/28), with the predominant symptoms being heartburn, regurgitation, endoscopic criteria-LA classification (3/28), biopsy criteria (2/28),24hpH criteria /Demeester scoring (2/28).

TABLE 4: LOS ANGELES CLASSIFICATION FOR GRADING ESOPHAGITIS [5]

GRADE	DESCRIPTION
A	One or more mucosal breaks confined to folds and < 5mm
B	One or more mucosal breaks confined to folds > 5mm
C	Mucosal breaks continuous between top of two mucosal folds but not circumferential
D	circumferential mucosal breaks

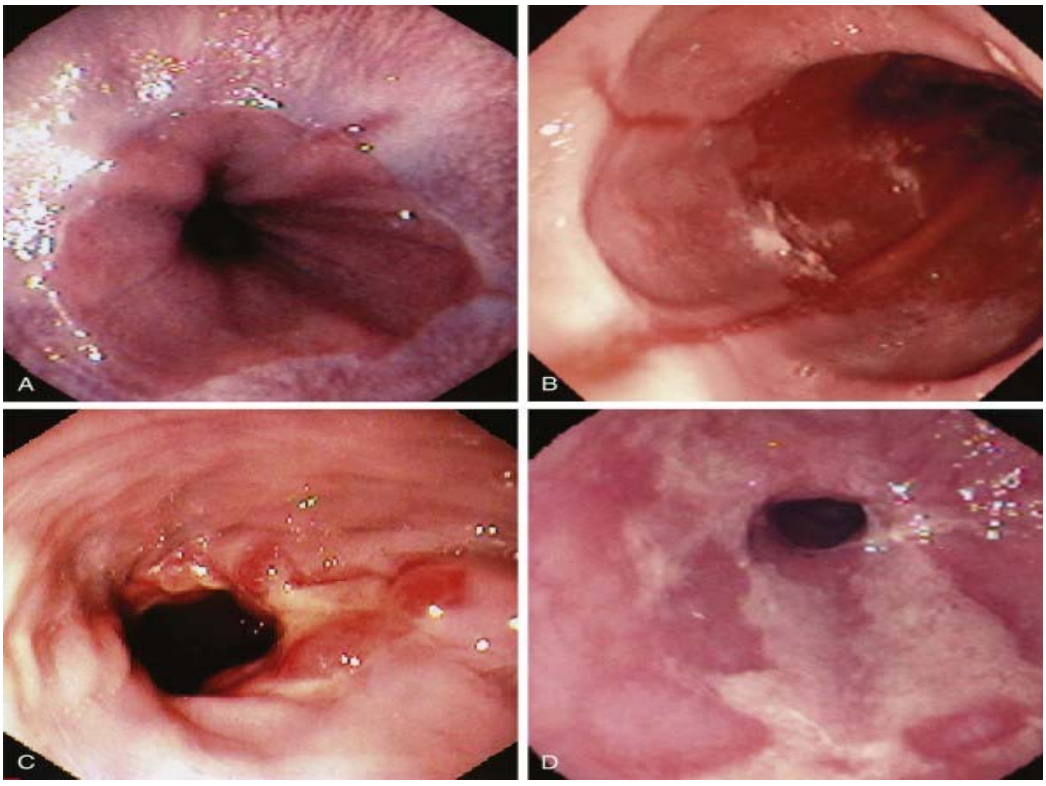


FIGURE 8 : LOS ANGELES CLASSIFICATION FOR GRADING ESOPHAGITIS

24h pH SCORING-DEMEESTER SCORE

Components

1 Upright reflux

2 Supine reflux

3 Total reflux

4 Number of episodes

5 Number of episodes longer than 5 min

6 Longest episode

Score > 14.7 is significant for reflux

BIOPSY CRITERIA

GERD was diagnosed if

1 Basal cell hyperplasia
2 Increased height of rete pegs } were present

All patients were selected to undergo gastric scintigraphy after application of specific inclusion and exclusion criteria.A written informed consent was taken from each patient after explaining that the procedure may take a time of 4 hours with need for intermittent scans, need to eat egg, enquiring regarding egg allergy, and radiation exposure. Patients who preferred vegetarian diet were given alternative test meal of idly and sambhar equivalent to 250Kcal labeled with technetium.

Inclusion Criteria

Age group : 18 -60 years

Typical symptoms of GERD

Exclusion Criteria

1 Peptic stricture of esophagus

2 Esophageal or gastric malignancy

3 Prior history of antireflux or gastric surgery

4 Pregnancy

5 Severe cardiorespiratory illness

6 Renal failure

7 Diabetes mellitus

GASTRIC SCINTIGRAPHY PROCEDURE

Gastric Scintigraphy was done using standard scintigraphic protocol.[41]All patients were on overnight fast and as per prior instructions were advised to stop agents that may interfere with gastric motility such as prokinetics, opioids, erythromycin for 2 days prior to the test.

TEST MEAL INTAKE

All patients were instructed to take 99m technetium sulfur colloid labeled low fat egg meal with two slices of bread and jam (0.5-1 mci Tc /255 Kcal). The meal was prepared by cooking egg as omelette with

incorporation of technetium sulfur colloid(0.5-1mci) into omelette. Then a bread omelette sandwich was made with adding of jam (30g-strawberry flavor) over the bread. Patients were advised to take the meal within 10 minutes and serial imaging begun.Two patients who preferred vegetarian meal were given two idlis(small size with a cup of sambar with total calories equivalent to 250Kcal) labeled with technetium sulfur colloid(0.5-1mci)

SERIAL IMAGING

Patients then underwent serial imaging with GE Millennium MPR SPECT gamma camera at 0 min,60 min,120 min,180 min, 240min after test meal intake Images were obtained in a format of 64 x 64 pixels using a general purpose collimator with photopeak settings being 20% at 120 keV for 99m Tc. Images were obtained in same position in each patient, with sitting position being preferred. The patients position remained constant during entire study.

IMAGE ANALYSIS

Assessment of Global Gastric Emptying

After imaging, analysis for gastric retention done by applying irregular region of interest tool (ROI) over entire stomach, including

proximal and distal stomach as a whole with careful exclusion of intestinal loops.

Assessment of Regional Gastric Emptying

For assessment of regional gastric emptying, irregular ROI (Region of Interest) tool was applied over proximal and distal stomach separately. ROI are drawn on 0 min and 240 min images. Regional gastric emptying includes separate ROI for antrum and fundus of stomach. Gastric counts of tracer activity at 240 min divided by gastric counts of tracer activity at 0 minutes and expressed as percentage gives percentage retention of food at 240min. Gastroparesis was considered significant at gastric retention value of >10 % at 240 min. 240 minute value was taken for assessment of gastroparesis.

GRADING OF GASTROPARESIS

Gastroparesis was graded based on 240 min value as

Mild : 11-20 %

Moderate : 21-35 %

Severe : 36-50%

Very Severe : >50%

Regional gastric retention also was expressed as percentage of initial counts remaining in fundus, antrum after drawing specific ROI .

GCSI -GASTROPARESIS CARDINAL SYMPTOM INDEX

Gastroparesis cardinal symptom index(GCSI) was assessed after ingestion of test meal as presence of post prandial fullness, nausea/vomiting, abdominal bloating. It was considered significant when 2 out of 3 symptoms were positive. The subscales were not analyzed separately. Statistical Analysis was then done using Fisher Exact Chi Square test, Binomial test (SPSS VERSION 17.0).

RESULTS

1. AGE DISTRIBUTION AND SYMPTOMATIC PERIOD OF GERD CASES

This Study included a total of 28 cases

TABLE 5

Variable	Age (years)	Symptomatic Period (Months)
Number	28	28
Mean	34.57	20.36
Median	35.00	12.00
Std. Deviation	8.846	25.519
Minimum	19	3
Maximum	53	120

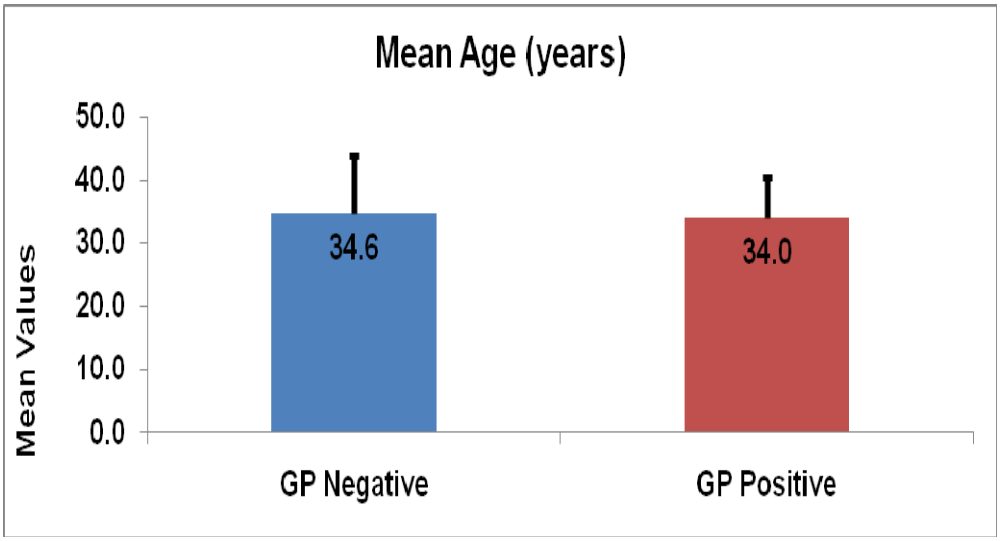


FIGURE 9 : AGE DISTRIBUTION

2. GENDER DISTRIBUTION

This study had equal representation of males and females

TABLE 6

Gender	Frequency	Percentage
Male	14	50.0
Female	14	50.0
Total	28	100.0

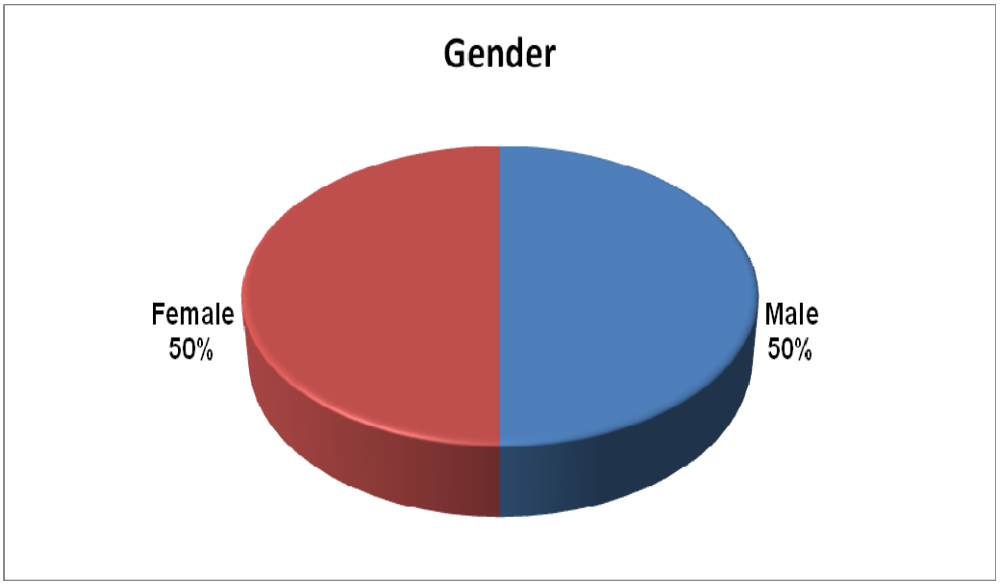


FIGURE 10 :GENDER DISTRIBUTION

3. GERD DIAGNOSIS BY DIFFERENT CRITERIAE

All patients enrolled in the study had symptomatic criteria fulfilled(100%). In addition 5 cases had endoscopic evidence of esophagitis(17.9%), 2 cases had biopsy evidence of GERD as per defined criteria(7.1%),2 cases who had undergone 24hour pH study were diagnosed to have GERD(7.1%).Of these two patients one had severe alkaline reflux with demeester pH score of 35 and another patient had severe acid reflux with demeester pH score of 34.4

TABLE 7 : GERD AND OGD

GERD and OGD	Frequency	Percentage
NO	23	82
YES	5	18
Total	28	100.0

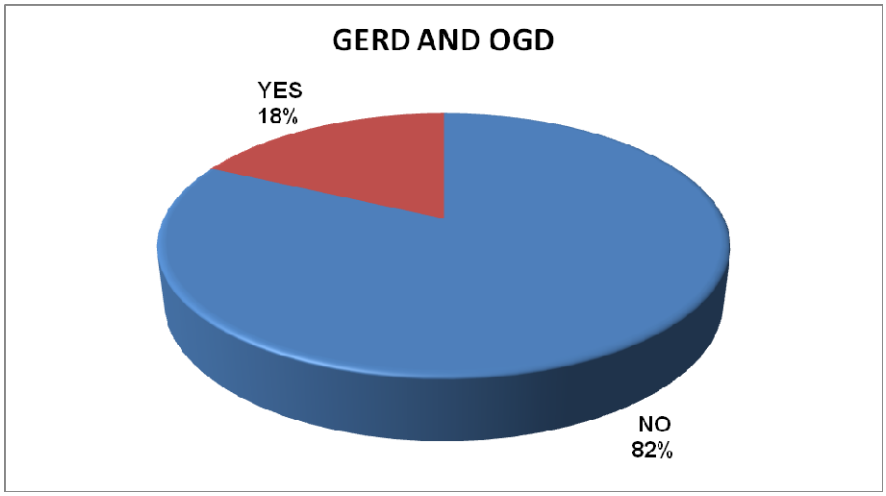


FIGURE 11: ENDOSCOPIC ESOPHAGITIS PREVALENCE

TABLE 8 : GERD AND BIOPSY

GERD and Biopsy	Frequency	Percentage
NO	26	92.9
YES	2	7.1
Total	28	100.0

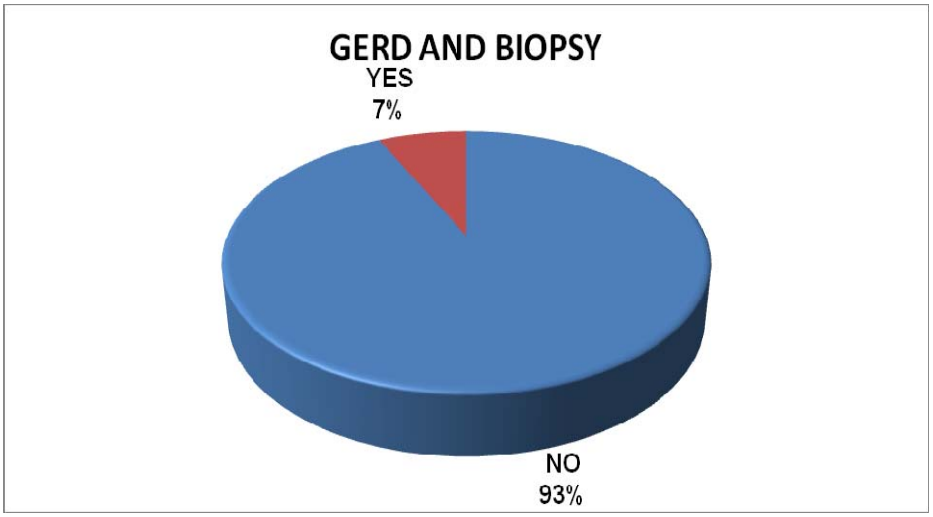


FIGURE 12: GERD AND BIOPSY

TABLE 9 : GERD AND 24 HOUR pH STUDY

GERD and pH study	Frequency	Percent
NO	26	92.9
YES	2	7.1
Total	28	100.0

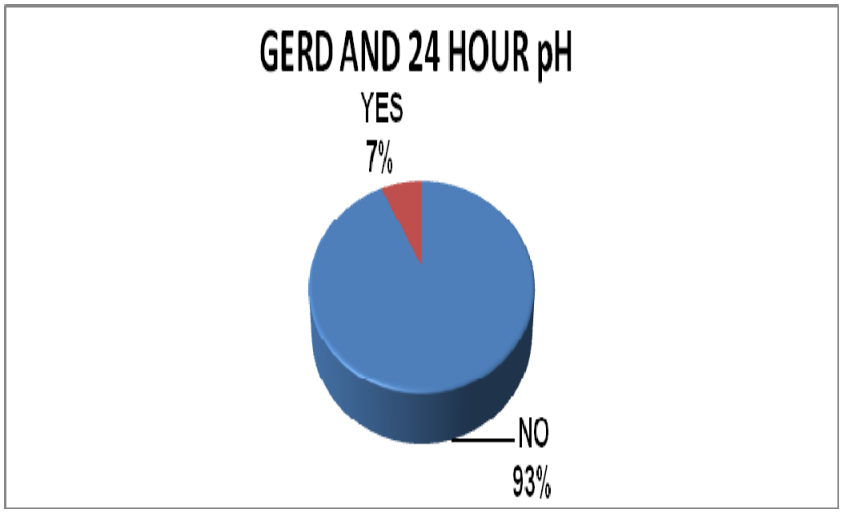


FIGURE 13 : GERD AND 24 HOUR pH STUDY

4. UPPER GI ENDOSCOPY FINDINGS IN ALL PATIENTS:

57.1% had normal endoscopy and rest of patients had abnormalities. Two patients had suspicious nodules in distal esophagus which were biopsied. Biopsy showed histological features of GERD but no evidence of metaplasia or dysplasia. Hiatus hernia was present in three cases (prevalence 10.7%) and one of those patients had Cameron ulcer and Schatzki B ring which is considered to be form fruste of GERD.

TABLE 10 : UPPER GI ENDOSCOPIC FINDINGS IN ALL CASES

OGD	Frequency	Percent
Normal	16	57.1
Losangeles – grade A/C	3	10.7
Pangastritis	3	10.7
Antral gastritis	1	3.6
Nodule in distal esophagus- Biopsy taken	2	7.1
Hiatus hernia	2	7.1
Hiatus hernia/cameron ulcer/ schatzki b ring	1	3.6
Total	28	100.0

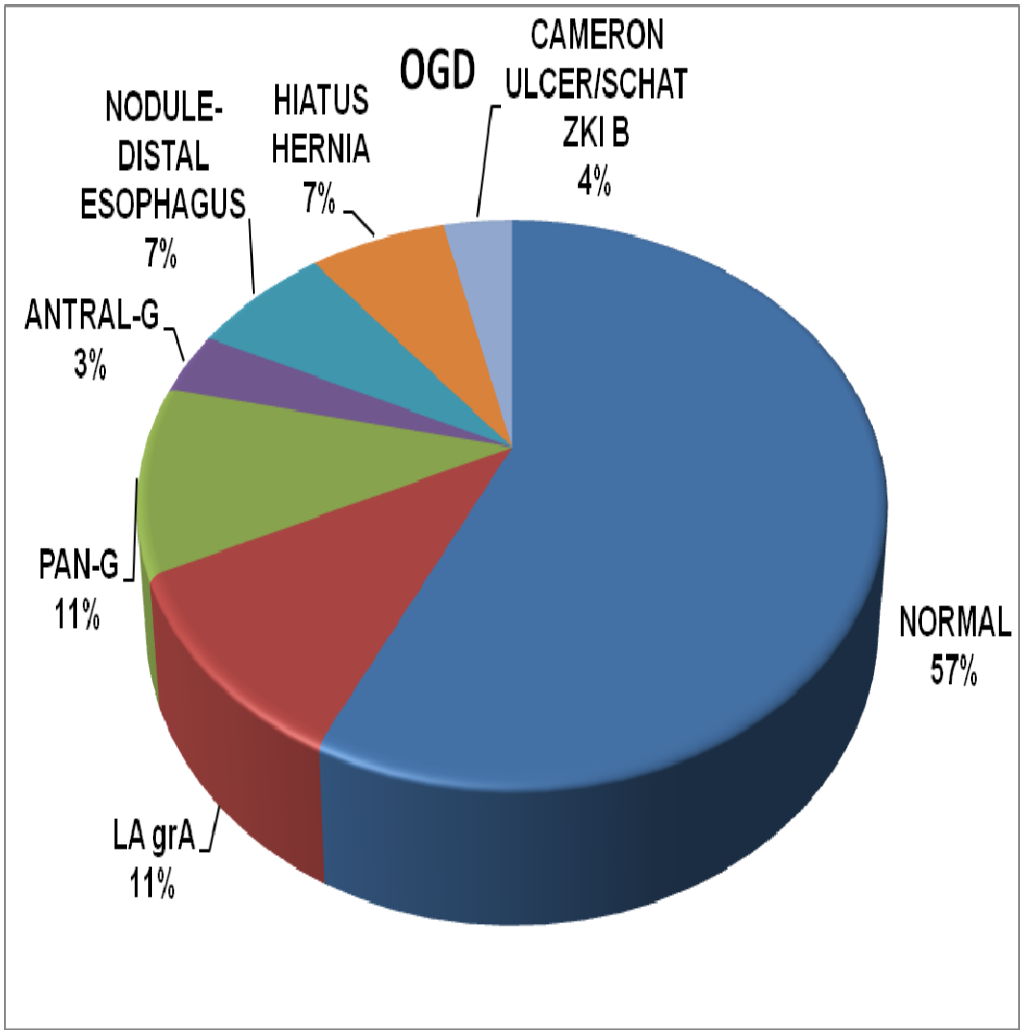


FIGURE 14 :UPPER GI ENDOSCOPIC FINDINGS IN ALL CASES

5. PPI USE

Patients were already on PPI in 53.6% and rest were on antacids, H2 receptor antagonists like tablet ranitidine 150mg b.d These patients were advised to take PPI since their enrollment into study.

TABLE 11 : PPI USE IN ALL CASES

PPI USE	Frequency	Percent
NO	13	46.4
YES	15	53.6
Total	28	100.0

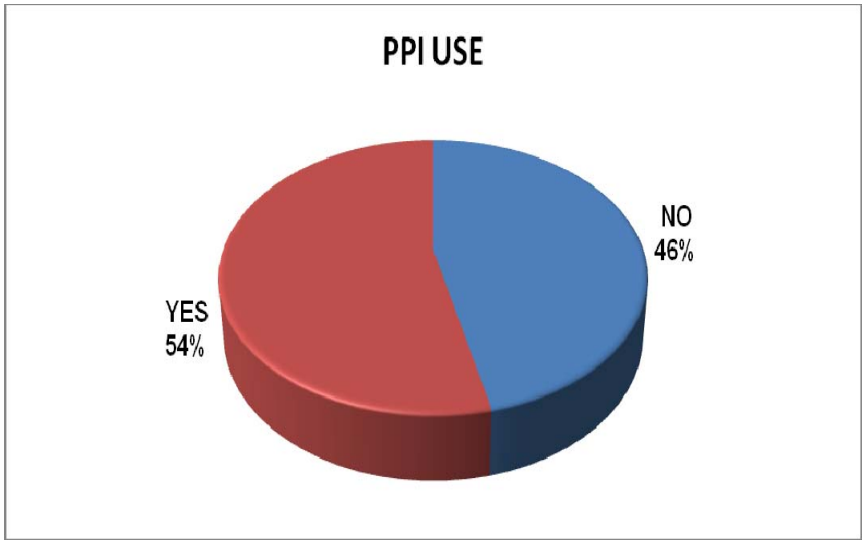


FIGURE 15 : PPI USE IN ALL CASES

6. PPI SENSITIVITY

96.4% of patients were sensitive to PPI. Only one patient demonstrated to have severe alkaline reflux on 24h pH study, had heartburn refractory to PPI therapy. He also had positive gastroparesis cardinal symptom index.

TABLE 12 : PPI SENSITIVITY PREVALENCE

PPI Sensitive Cases	Frequency	Percent
YES	27	96.4
NO	1	3.6
Total	28	100.0

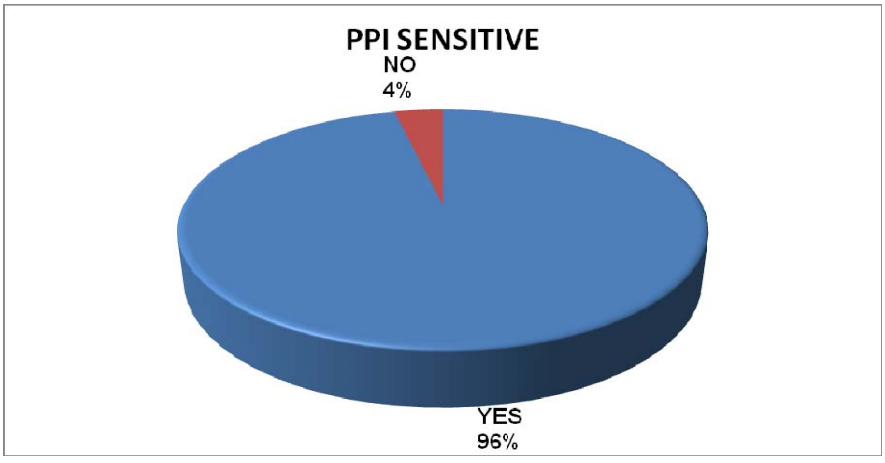


FIGURE 16 : PPI SENSITIVITY PREVALENCE

7. GASTROPARESIS PREVALENCE

Gastroparesis was noted to have a prevalence of 10.7% (being positive in three out of twenty eight cases)

TABLE 13 : PREVALENCE OF GASTROPARESIS

Gastroparesis	Frequency	Percentage
Negative	25	89.3
Positive	3	10.7
Total	28	100.0

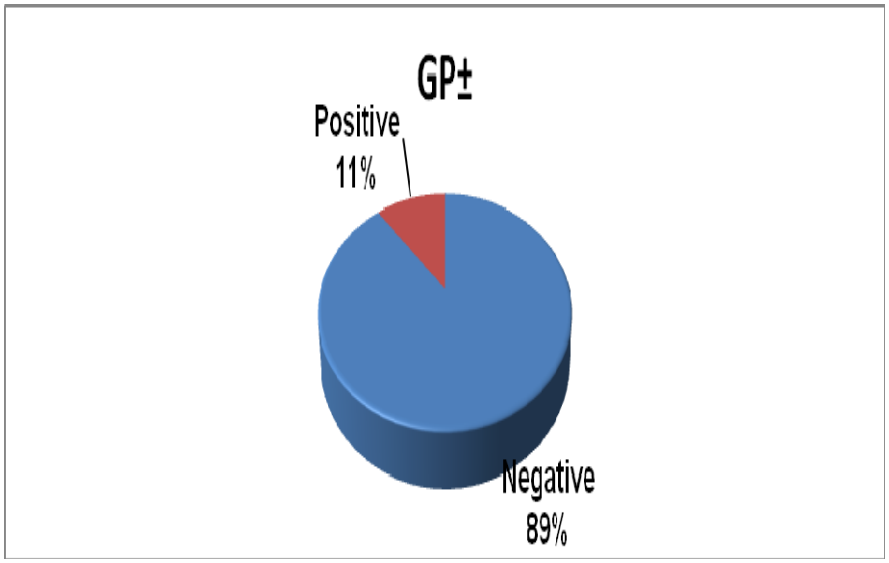


FIGURE 17 : PREVALENCE OF GASTROPARESIS

8. INDIVIDUAL ANALYSIS OF DELAYED GASTRIC EMPTYING IN THREE PATIENTS

GRADE OF GASTROPARESIS

All three patients who were found to have gastroparesis had mild gastroparesis as per grading of gastroparesis.

TABLE 14

% Retention at 4 H	Frequency	Percent
10.16	1	3.6
11.60	1	3.6
12.60	1	3.6
Total	3	10.7

FUNDAL VERSUS ANTRAL RETENTION OF MEAL

Out of three patients who had gastroparesis, fundal retention predominated in two cases and antral retention predominated in one case.

TABLE 15

Case	Fundal Retention (%)	Antral Retention (%)
1	5.72	4.44
2	5.60	7.04
3	7.9	3.7

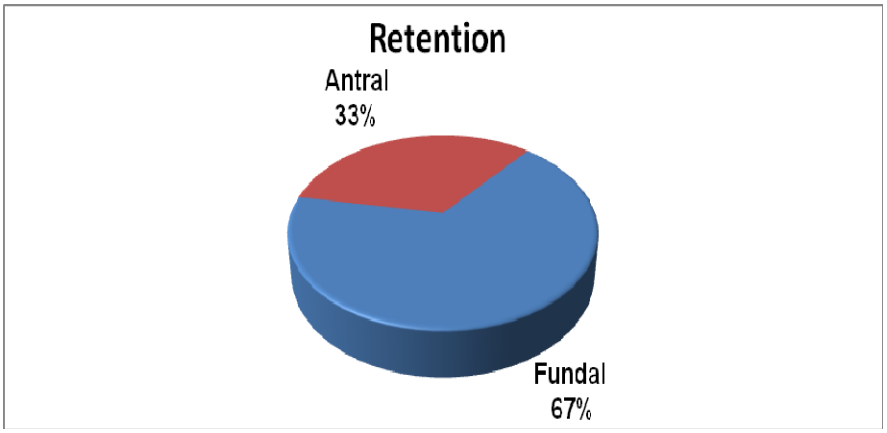


FIGURE 18 : FUNDAL VERSUS ANTRAL RETENTION

9. GASTROPARESIS CARDINAL SYMPTOM INDEX:(GCSI)

Gastroparesis Cardinal Symptom Index was positive in 5 cases (17.9%) and negative in 82.1 % cases. All patients who had positive GCSI had early satiety and abdominal bloating as symptoms.None presented with vomiting of test meal.

TABLE 16 : GCSI DURING SCINTIGRAPHY

GCSI	Frequency	Percentage
NEGATIVE	23	82.1
POSITIVE	5	17.9

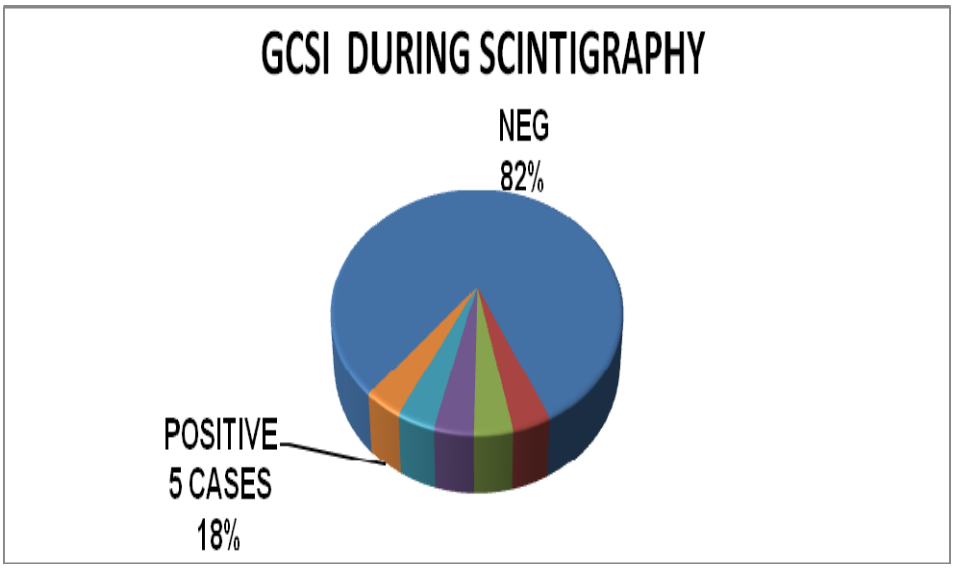


FIGURE 19 : GCSI DURING SCINTIGRAPHY

10. GENDER DIFFERENCE IN PREVALENCE OF GASTROPARESIS

Of the three patients with gastroparesis,two were females and one was male (66.7% versus 33.3%)

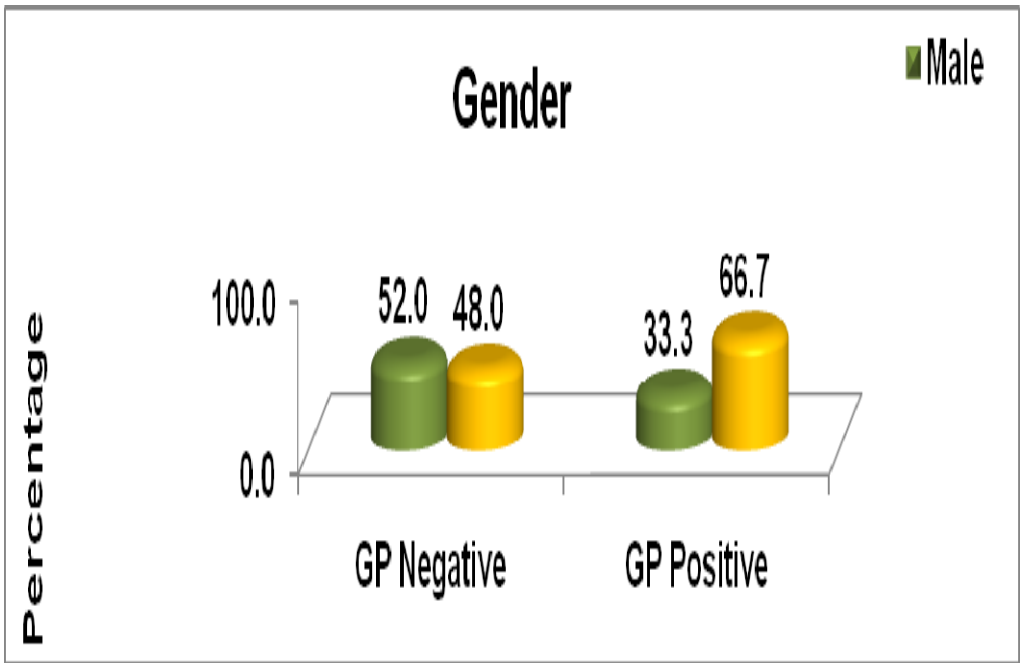


FIGURE 20: GENDER DIFFERENCE IN PREVALENCE OF GASTROPARESIS

11 CORRELATION BETWEEN GCSI AND GASTROPARESIS

GCSI was positive in five out of 28 cases whereas gastroparesis was present in only three out of 28 cases.Statistical analysis revealed lack of significant correlation between GCSI and gastroparesis.

TABLE 17 : CORRELATION BETWEEN GCSI AND GASTROPARESIS

GPSI during SCINTI * GP± Crosstabulation					
			GP±		
			Negative	Positive	Total
GPSI during SCINTI	Negative	Count	22	1	23
		% within GP±	88.0%	33.3%	82.1%
	Positive	Count	3	2	5
		% within GP±	12.0%	66.7%	17.9%
Total		Count	25	3	28
		% within GP±	100.0%	100.0%	100.0%

P value for correlation is 0.073 (NS,Fishers Exact Test) and is not significant indicating a poor correlation between GCSI and objective evidence of gastroparesis.

12 PREVALENCE OF GASTROPARESIS:SIGNIFICANCE

Based on the binomial test(p=0.5),the prevalence of gastroparesis (10.7%) is significant at $p < 0.005$

FIG 21(a) NORMAL DISTAL ESOPHAGUS

FIG 21(b) DISTAL ESOPHAGITIS –GRADE C

(LA CLASSIFICATION)

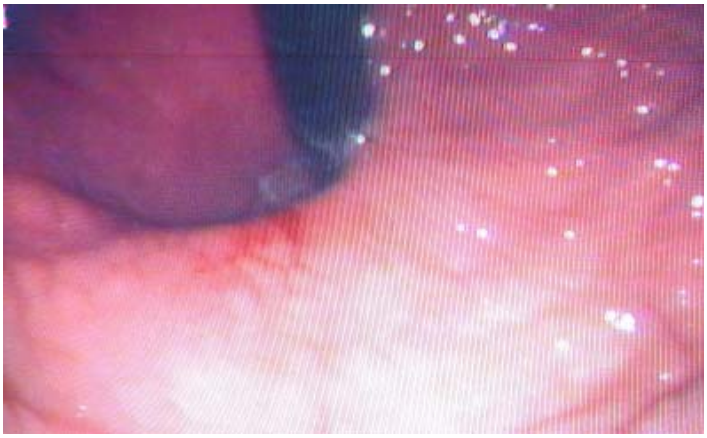
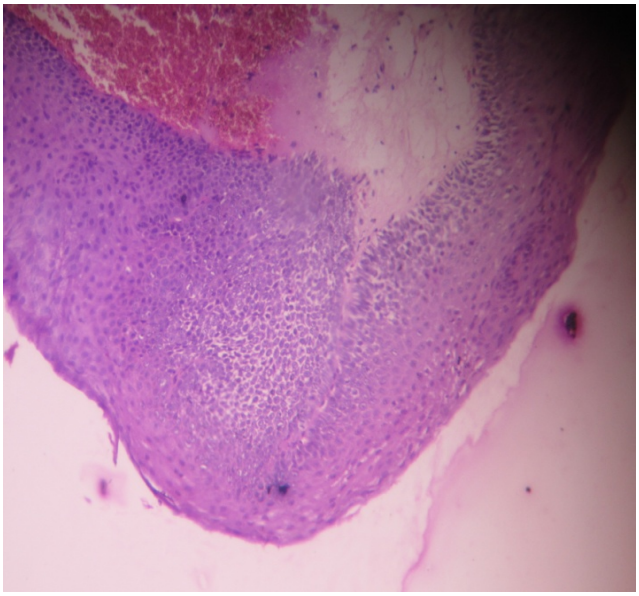


FIG 21(c) LAX LES IN HIATUS HERNIA

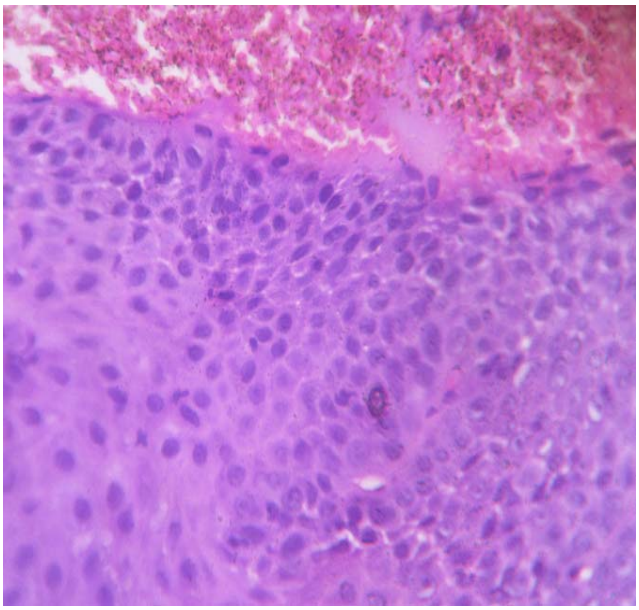
FIGURE 22 GERD AND BIOPSY

This biopsy taken from nodule in distal esophagus shows features of squamous epithelium with basal cell hyperplasia suggestive of GERD

LOW POWER VIEW



HIGH POWER VIEW



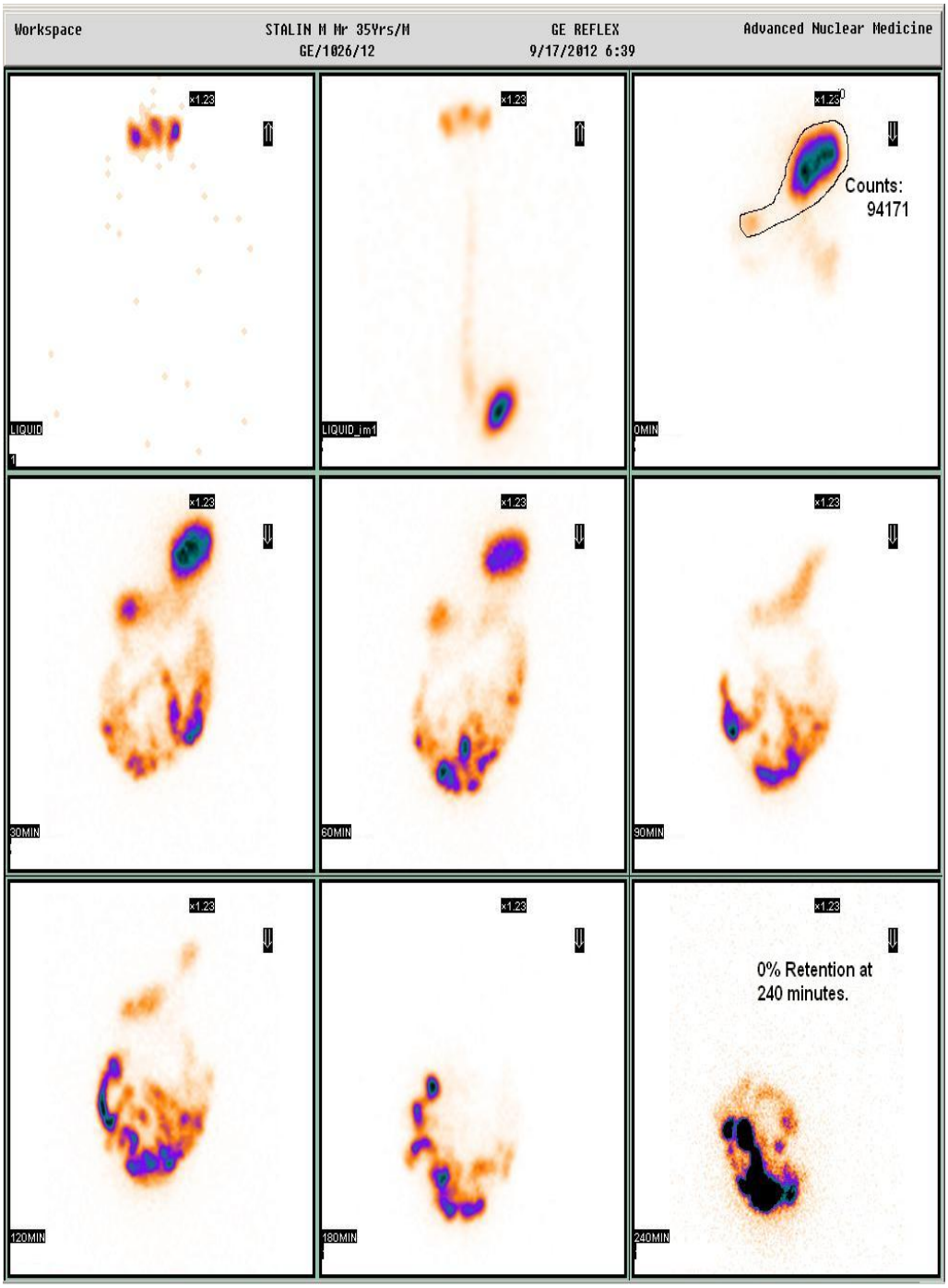


FIGURE 23 :NORMAL GASTRIC EMPTYING (AT 4 HOURS)

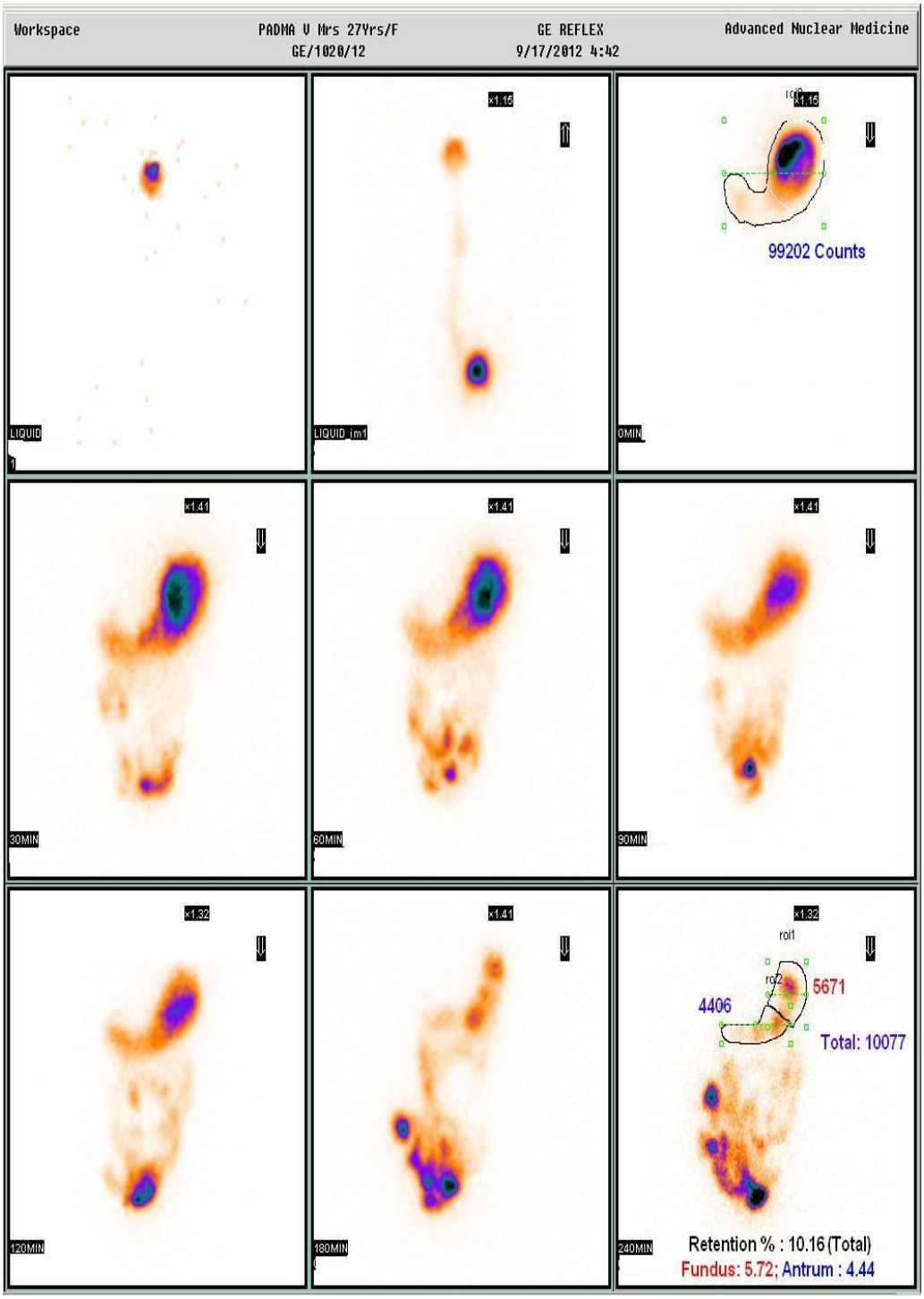


FIGURE 24: GASTROPARESIS CASE 1

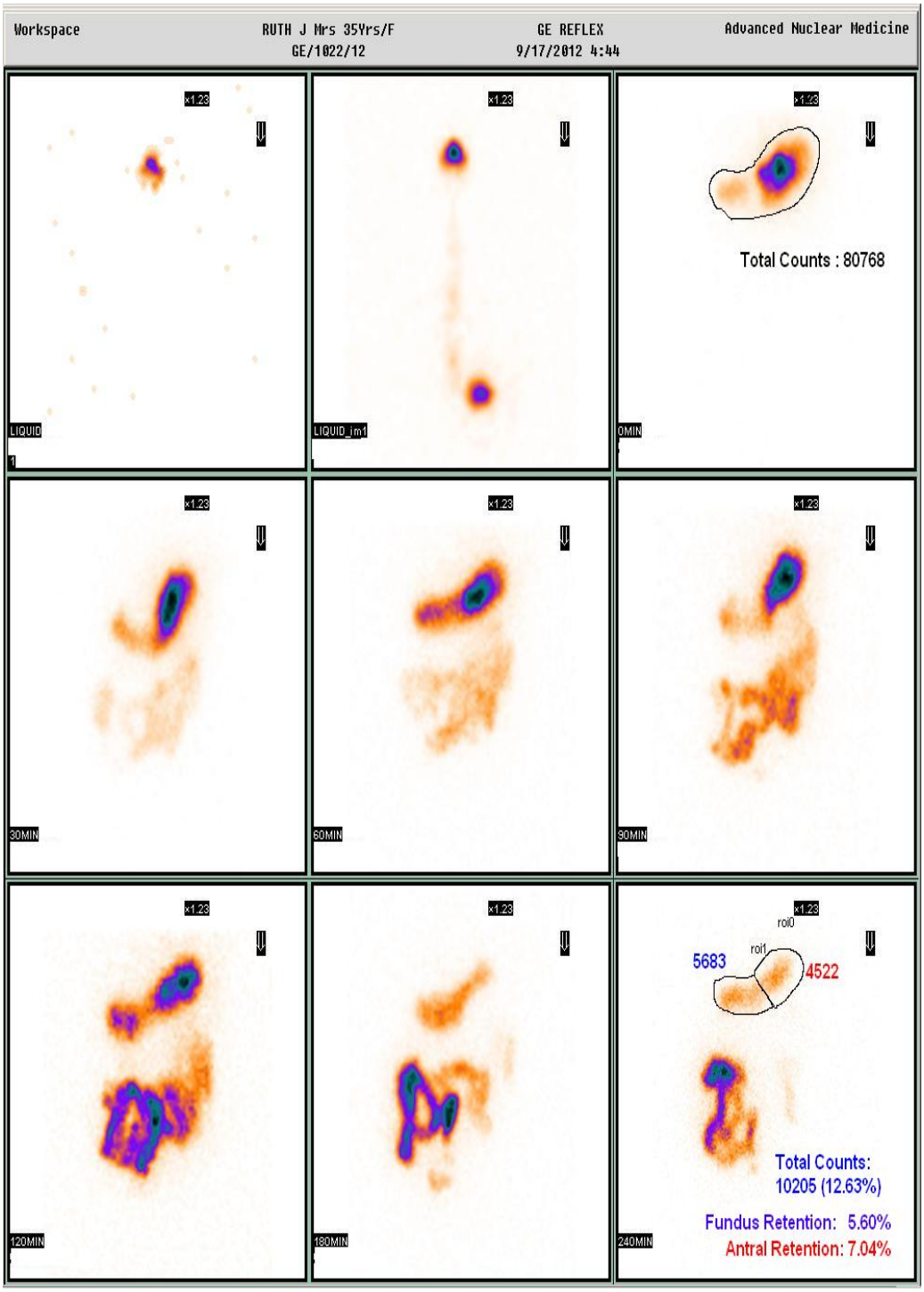


FIGURE 25:GASTROPARESIS CASE 2

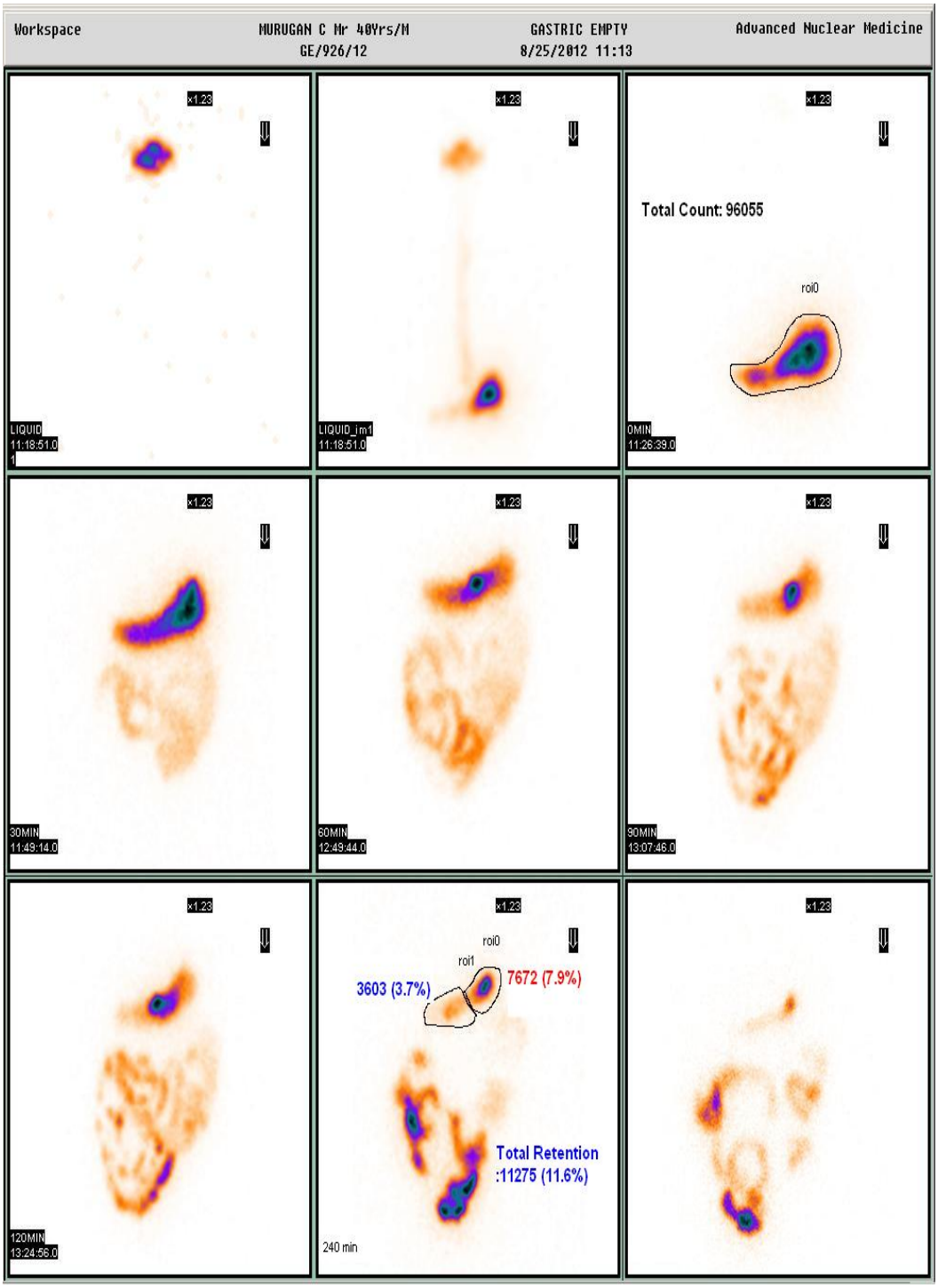


FIGURE 26: GASTROPARESIS CASE 3

DISCUSSION

Typical office cohort of GERD patients may present with symptoms heart burn and regurgitation, but may have additional symptoms of postprandial fullness, nausea, abdominal bloating. Alternatively, patients may also present as nonresponders to proton pump therapy. This group of patients represent overlap cases with functional dyspepsia and usually account for one third of all GERD cases.[6] The diagnosis of such overlap cases requires high index of suspicion since all symptoms may be attributed to GERD alone. Once the diagnosis of such overlap is entertained, further testing is mandatory to confirm the suspicion .It is imperative to rule out organic causes of dyspepsia by performing upper gastrointestinal endoscopy. Screening endoscopy can also help categorize GERD into anyone of three categories namely erosive, nonerosive, complicated GERD. Biopsies as required for suspected barretts, may be essential but Schindlebeck NE et al have shown that there is no role for routine biopsy of lower esophagus in uncomplicated GERD[43] 24h ambulatory pH monitoring is also important in diagnostic workup as it is the current standard for diagnosis of GERD (including NERD). Also, Noh Y et al have shown significant association between NERD and functional dyspeptic

symptoms[18]. Once GERD is categorized into aforesaid categories, next step in uncomplicated cases would be a gastric emptying study since gastric emptying abnormalities are known to occur in patients with such overlap features. In particular, Gonlachanvit et al have shown in their seminal study that delayed gastric emptying and antral retention of test meal occur in cases of functional dyspepsia[20]. Gastric emptying may be studied by group of tests including gastric scintigraphy, functional ultrasonography, MRI. Marzio L et al have shown that functional ultrasound is useful mainly in assessment of liquid phase emptying study and that liquid emptying does not become abnormal till gastroparesis is severe.[11.] Functional ultrasound requires assumptions to be made regarding geometric shape of stomach and therefore may not be very accurate as a study for gastric emptying. MRI is evolving in assessment of gastric emptying and is also expensive.

Gastric scintigraphy for assessment of gastric emptying ,which came into clinical application since 1966,has evolved over past forty seven years to be considered the current gold standard. The advantages of scintigraphy include availability of international standard values for normal gastric emptying derived from the seminal study by Tougas et al[41] and that it can help assess gastroparesis as a dysfunction of whole stomach, fundus, antrum.This helps us to understand the

pathophysiology of functional dyspepsia in a better way, so that it may guide us to optimize therapy. Our study shows that the prevalence of idiopathic gastroparesis in uncomplicated, office cohort of GERD cases to be 10.7% as against prevalence of 25% shown by Koch KL et al[7] This variable prevalence has been attributed to differences in study methodology, variable patient selection criteria and inclusion of patients with diabetes mellitus, a known risk factor for gastroparesis.

The study done by Gonlachanvit et al had assessed gastric emptying in overlap cases and found that gastric emptying is delayed in 50% of overlap cases [20].They also report that distal gastric retention was prominent in overlap cases in contrast to GERD cases alone. In contrast, our study results show predominance of fundal retention of food in overlap cases.

Gastroparesis cardinal symptom index is a questionnaire applicable in patients with gastroparesis. This symptom complex questionnaire has three scales and nine subscales. Our study aimed to apply this questionnaire in all subjects, in the immediate postprandial period after ingestion of technetium labeled meal, since it was an ideal time to observe the symptoms and correlate it with occurrence of delayed gastric emptying. Interestingly, five patients satisfied two out of three scales of gastroparesis index within 30min after ingestion of test meal

but only two of them had objective evidence of gastroparesis. Statistical analysis of the same revealed only modest correlation between GCSI and scintigraphic demonstration of gastroparesis (p=0.073 Fischer Exact Test). This observation has important implications. Despite noting that patients had symptoms suggestive of gastroparesis, scintigraphy could not demonstrate delayed gastric emptying in three out of five patients who were positive for symptom index. Since we know that scintigraphy is a sensitive tool for detection of gastroparesis, the role of other pathophysiological factors such as visceral hypersensitivity, altered gut neurotransmission may explain symptoms in such patients. Also, the lack of correlation between GCSI and gastroparesis mandates need for gastric scintigraphy to objectively rule in or rule out gastroparesis.

All three cases of gastroparesis seen in our study were only of mild grade (10 – 20 % retention). This is in concordance with study done by Sarnelli et al which evaluated gastric emptying in GERD cases.[25]

Also, in our study ,gastroparesis was diagnosed in two females and one male (66.7vs33.3%) This female preponderance of gastroparesis has been noted by Soykan I et al who demonstrated gastroparesis with 82% prevalence in females compared to 18% in

males. [44] Indeed Gill RC et al demonstrated delayed gastric emptying in females especially during luteal phase of menstrual cycle [45] In contrast, a study done by Walsh J W et al that tried to correlate gastroparesis with estrogen, progesterone values had not found significant correlation[46].

In our study, one patient had PPI nonresponsiveness(3.6% prevalence).This patient was initially responsive to PPI for a period of 2 years,then he had become gradually nonresponsive to PPI. This patient developed positive GCSI immediately after ingestion of test meal and objective evidence of gastroparesis(11.6%)with fundal predominance of meal retention. Interestingly the patient had ambulatory pH evidence of severe alkaline reflux with pH score of 35.This patient was treated with PPI and prokinetics (T.Domperidone 10mg b.d) . He had partial symptom improvement.The therapeutic impact of diagnosing gastroparesis in patients with GERD thus has two caveats.First,gastroparesis may impair treatment efficacy of PPIs. Delay in gastric emptying of premeal PPI may affect its delivery to effector site, namely the proton pumps at appropriate time and thus impair its efficacy. Thus, PPI formulations that may release the drug faster than normal may be indicated in such cases. Two formulations tried include omeprazole immediate release tablets given reconstituted with water and lansoprazole oral dissolving formulation.[47] This may help overcome PPI nonresponsiveness. Secondly, prokinetics and drugs

useful in management of functional dyspepsia such as acotiamide, buspirone may have role in management of patients with gastroparesis. Prokinetics tried in past have been limited by side effects ,none more than the ideal prokinetic cisapride which was removed from market in view of propensity to cause cardiac dysrhythmias.The drug which has captured recent attention is acotiamide which acts by dual mechanism of inhibition of muscarinic autoreceptors in enteric nervous system and also by inhibition of acetylcholinesterase thereby augmenting parasympathetic transmission.

Phase III trials of the drug at a dose of 100mg t.i.d for 4 weeks have shown good response in functional dyspepsia patients with few side effects,including hypertriglyceridemia[48]Further studies are needed to incorporate this drug into routine clinical practice.Thus it is very clear that diagnosis of gastroparesis using gastric scintigraphy in GERD cases presenting with FD overlap is mandatory to help guide further therapy in this group of patients who may not be PPI responsive in the long run.

CONCLUSIONS

1 There is a significant prevalence of gastroparesis in gastroesophageal reflux disease (10.7%).

2 All cases of gastroparesis detected in GERD patients were of mild grade.

3 Fundal retention predominated over antral retention in cases with gastroparesis (66.7% versus 33.3%).

4 Gastroparesis was found predominantly in female patients (66.7% vs33.3%).

5 The Correlation between gastroparesis Cardinal symptom index and scintigraphic gastroparesis was not significant.

BIBLIOGRAPHY

1 Nimish V; Montreal definition and classification of GERD:A global evidence based consensus. (American journal of Gastroenterology: 2006; 101: 1900-1920)

2 Dent J, Armstrong D, Delaney B, et al. Symptom evaluation in reflux disease – Gut 2004; 53(Suppl 4): IV 1-24.

3 Caviglie R, Rebols M, MaggianoN, et al. Dilated intercellular spaces of esophageal epithelium in non erosive reflux disease patients with physiological esophageal acid exposure; American journal of Gastroenterology 2005; 100: 543-8

4 Johnsson F, Joelsson B, Gudmurdsson K et al. Symptoms and endoscopic findings in diagnosis of gastro esophageal reflux disease. Scand journal of Gastroenterology 1987; 22:714-8

5 Lundell LR, Dent J, Bennett JR et al; Endoscopic assessment of esophagitis clinical and functional correlates and further validation of Los Angeles classification; Gut 1999; 45; 172-80

6 Tack J, Talley NJ, Camiller M et al; functional GI disorder: Jn: Drussman DA Rome III FGID: Lawrence, Kansas: Allen Press: 2006; 419-86)

7 Koch KL, XUL, Naar M: Gastric myoelectrical and emptying activity in patients with GERD and dysmotility litre FD (GERD+). Effect of water load test: American journal of Gastroenterology 2010: 96: 526.

8 Quigley EM: GERD: The roles of motility in pathophysiology and therapy American journal of Gastroenterology (1993): 88: 1649-51.

9 Penagini R, Hebbard G, Horowitz M et al: Motor function of proximal stomach and visceral perception in GERD: Gut 1998; 42: 251-7.

10 Lavenstein TC, Vugt fm et al: Time resolved 3D MR imaging of gastric imaging American journal of Roentgenology 2003; 180: 1305-1310.

11 Marzio L, G: acobbe A et al. Evaluation of use of USG in study of liquid gastric emptying American journal of Gastroenterology 1989; 84:496-500

12 Bhatia SJ,Reddy DN, Ghosal UC et al: ISG Task force report: Epidemiology and symptom profile of GER in Indian population: Indian Journal of Gastroenterology 2011;30:doi: 10.1007/s12664-011-0112

13 Kumar S,Sharma S,Norboo T et al: Population based study to assess prevalence and risk factors of Gastroesophageal Reflux in high altitude area :Indian journal of gastroenterology 2011:30:doi: 10.1007/ s12664-010-0066-4

14 Grainger SL,Klass HJ et al: Prevalence of dyspepsia: Epidemiology of overlapping symptoms:Post graduate medicine 1994;70:154-161

15 Singh V,Trikha B,Nain,Vaipheik:Epidemiology of H pylori and Peptic Ulcer in India.Journal of Gastroenterology and Hepatology 2002;17:659-65

16 Ghosal UC,Abraham P:Epidemiological and Clinical profile of IBS:Report of ISG Task force.Indian Journal of gastroenterology 2008:27:22-28

17 Modlin I M et al:Diagnosis and management of NERD-the Vevy NERD Consensus group;Digestion 80,74-88 (2009).

18 Noh Y,Jung H,Kim SE:Overlap of erosive and nonerosive diseases with FGID according to Rome III Criteria Journal of Neurogastroenterology Motility 16,148-156(2010)

19 Mittal R,Holloway R,Penagini R,Dent J-Transient Lower Esophageal Sphincter relaxations :Gastroenterology 109;601-610 (1995)

20 Gonlachanvit S,Maurer AH,Fisher RS:Regional Gastric emptyingabnormalities in GERD and Functional dyspepsia: Neurogastroenterology Motility 18,894-904(2006)

21 Miyamoto M,Manabe N:Efficacy of addition of prokinetics for PPI Resistant NERD patients:Significance of Frequency Scale for symptom of GERD(SSG) on decision of treatment strategy; Internal Medicine :49,1469-1476 (2010)

22 Holtmann G,Siffert W et al;G Protein beta 3 subunit 825 CC is associated with Functional dyspepsia;Gastroenterology 2004; Volume 126,Issue 4,971-979

23 De Vries D R,Ter Linde JJ,Samson M GERD is associated with C 825 T Polymorphism in the G Protein Beta 3 Subunit Gene GNB3 :American Journal of Gastroenterology 2009;104:281-285

24 Tack J et al: Prevalence of acid reflux in Functional dyspepsia and its association with symptom profile Gut 2005;54:1370-1376.

25 Sarnelli G et al:Symptoms associated with impaired gastric emptying of solids and liquids in Functional dyspepsia: American Journal of Gastroenterology 1998 ;783-788

26 Van Zanten et al:Esomeprazole 40mg O.D in patients with functional dyspepsia;ENTER TRIAL:American Journal of Gastroenterology 2008;101:2096-2106

27 Van Rensburg G et al Efficacy and Safety of Pantoprazole 20mg O D in patients with ulcer like dyspepsia: Curr Med Res Opin 2008; 24 :2009-2018

28 Wang W H et al:Effects of PPI on Functional dyspepsia: Metaanalysis of RCTs:Clinical Gastroenterology and Hepatology 2007 ;5:178-185

29 Vakil N et al : Tegaserod treatment for functional dyspepsia: Results of two randomized controltrials:American Journal of Gastroenterology 2008:101;1906-1919

30 Holtman G, Talley NJ et al: A placebo controlled trial of Itopride in Functional dyspepsia : New England Journal of Medicine 2006: 354;832-840

31 Tack J: Gastric motor disorders : Best Practice and Research Clinical Gastroenterology 2007 ; Vol 21:Number 4:pp633-644:doi 10.1016

32 Beaumont W:Experiments and Observations on gastric juice: Plattsburgh FF Allen ,1883

33 Cannon WB:The movements of Stomach studied by Roentgen Rays: American Journal of physiology1898;1:359-382

34 Feldman M ,Smith HJ,Simon TR: Gastric emptying of solid radioopaque markers : Studies in healthy subjects and diabetic patients:Gastroenterology 1984; 87:895-902

35 Gjjriffith GH,Owen GM et al:Measurement of gastric emptying rate using Cr51 :Lancet 1966:4:1244-1245

36 J .H.Meyer I.L.Mcgregor 99mTc tagged chicken liver as a marker of solid food in human stomach-Digestive diseases and Sciences:1976:Vol 21;4:296-304

37 Leb G,Lipp R et al: Criteria for labeled meals for gastric emptying studies in Nuclear Medicine :Eur J Nucl Med:1993;20:185-186

38 Miller G,Palmer KR et al:Smoking delays gastric emptying of solids: Gut 1989;30:50-3

39 Fraser R,Horowitz M,Maddox A:Hyperglycemia slows gastric emptying in Type 1 diabetes mellitus:Diabetology 1990;30: 675-680

40 Consensus Recommendation for gastric emptying scintigraphy: A joint report of American Neurogastroenterology and Motility Society and The Society of Nuclear medicine:Thomas L Abell et al: American Journal of Gastroenterology 2008 ;103:753-763

41 Tougas G et al:Assessment of gastric emptying using low fat meal: Establishment of international control values ;American Journal of gastroenterology 2000 ; 95:1456-1462

42 Revicki DA,Rentz A M :Development and Validation of patient assisted gastroparesis symptom severity measure:Aliment Pharmacol Ther 2003;18:141-150

43 Schindlbeck NE,Wiebecke B :Diagnostic value of histology in NERD: Gut 1996;39:151

44 Soykan I ,Sivri B et al: Demography, Clinical characteristics, psychological profiles, treatment and longterm followup of patients with gastroparesis: Digestive Diseases Sciences 1998;43:2398-2404

45 Gill RC,Murphy PD:Effect of menstrual cycle on Gastric emptying:Digestion 1987;36:168-174

46 Walsh JW, Hasler WL,Owyang C et al:Progesterone and Estrogen are potential mediators of gastric slow wave dysrhythmias in nausea of pregnancy: American Journal of Physiology 1996:270:G 506-14

47 Scarpignato C,Pelosini I et al:Acid Supression Therapy:Where do we go from here? Dig Dis Sci 2006;24:11-46

48 Kei Matsueda et al:A placebo controlled trial of acotiamide for meal related symptoms of functional dyspepsia :Gut 2012;61:821-828.

GLOSSARY / ACRONYMS

GERD	:	GASTRO ESOPHAGEAL REFLUX DISEASE
LES	:	LOWER ESOPHAGEAL SPHINCTER
TLOSR	:	TRANSIENT LOWER ESOPHAGEAL SPHINCTER RELAXATIONS
GE	:	GASTRIC EMPTYING
ROI	:	REGION OF INTEREST
GCSI	:	GASTROPARESIS CARDINAL SYMPTOM INDEX
FD	:	FUNCTIONAL DYSPEPSIA
PPI	:	PROTON PUMP INHIBITOR
GPCR	:	G PROTEIN COUPLED RECEPTOR
ICC	:	INTERSTITIAL CELLS OF CAJAL
GM	:	GEOMETRIC MEAN

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு

"உணவுக்குழாய் நோயினால் பாதிக்கப்பட்டவர்களைப் பற்றிய ஆய்வு"

ஆராய்ச்சி நிலையம் : இராஜீவ் காந்தி அரசு பொது மருத்துவமனை,
சென்னை மருத்துவக் கல்லூரி,
சென்னை - 03.

பங்கு பெறுவரின் பெயர் :

பங்குபெறபவரின் எண் :

பங்கு பெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். எனது உடல் நலம்பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கதிற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்து அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

இந்த ஆய்வில் எனக்கு இரத்தப் பரிசோதனை, வயிறு ஸ்கேன், உள்நோக்கி பரிசோதனை (என்டோஸ்கோபி), கதிர் இயக்க பரிசோதனை (நியூக்ளியர் ஸ்கேன்) ஆகிய பரிசோதனைகள் செய்துகொள்ள முழுமனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவனைக்கு வரும் நோயாளிகளில் உணவுக்குழாய் நோயினால் பாதிக்கப்பட்டவர்கள் குறித்த ஆய்வு இங்கு நடைபெற்று வருகிறது.

நீங்களும் ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களை பங்கேற்க வைத்து அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களின் நோயின் ஆய்வறிக்கையோ, சிகிச்சைக்கோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

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ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

INFORMED CONSENT FORM

Title of the Study

Gastroparesis in Gastroesophageal reflux disease-prevalence and assessment using gastric scintigraphy

Name of the Participant:

_____

Name of the Investigator : Dr. Arvind . M.A

Name of the Institution : Madras Medical College.

Documentation of the informed consent

I _____ have read the information of this form (or it had been read to me). I was free to ask any questions and they have been answered. I hereby give my consent to be included as a participant in Gastroparesis in Gastroesophageal reflux disease-prevalence and assessment using gastric scintigraphy

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

Name and signature / thump impression of the participant

Name _____ Signature _____ Date____

Name and signature of impartial witness (required for illiterate patients):

Name _____ Signature _____ Date____

Address and contact number of the impartial witness:

Name and signature of the investigator or his representative obtaining consent:

GASTROPARESIS IN GERD-PREVALENCE AND ASSESSMENT

USING GASTRIC SCINTIGRAPHY-PROFORMA

Name		
GE No		
Age		
Gender		
Address		
Diagnosis		
Phone Number		
Date		
History	Heart burn Nausea/Vomiting Post cibal fullness Alarm symptoms Drug history Pregnancy History of antireflux surgery History of gastric surgery History of diabetes Any co morbid illness	

Examination	Vital signs General examination Per abdomen Other system	
Investigations	Fasting blood sugar Post prandial blood sugar Hemogram Renal function test Upper gi endoscopy Gastric scintigraphy	
Gastric scintigraphy	Imaging time 0 h 1h 2h 4h	**%RETENTION**
Gastroparesis	Present	

	Absent If present Grade Fundal dysfunction Antral dysfunction Vomiting of meal (Y/N) Any unusual findings	

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Arvind M.A
PG in DM Medical Gastroenterology
Madras Medical College, Chennai -3

Dear Dr. Arvind M.A

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Gastroparesis in gastroesophagealreflux disease – incidence and assessment using gastric scintigraphy" No.06062012.

The following members of Ethics Committee were present in the meeting held on 19.06.2012 conducted at Madras Medical College, Chennai -3.

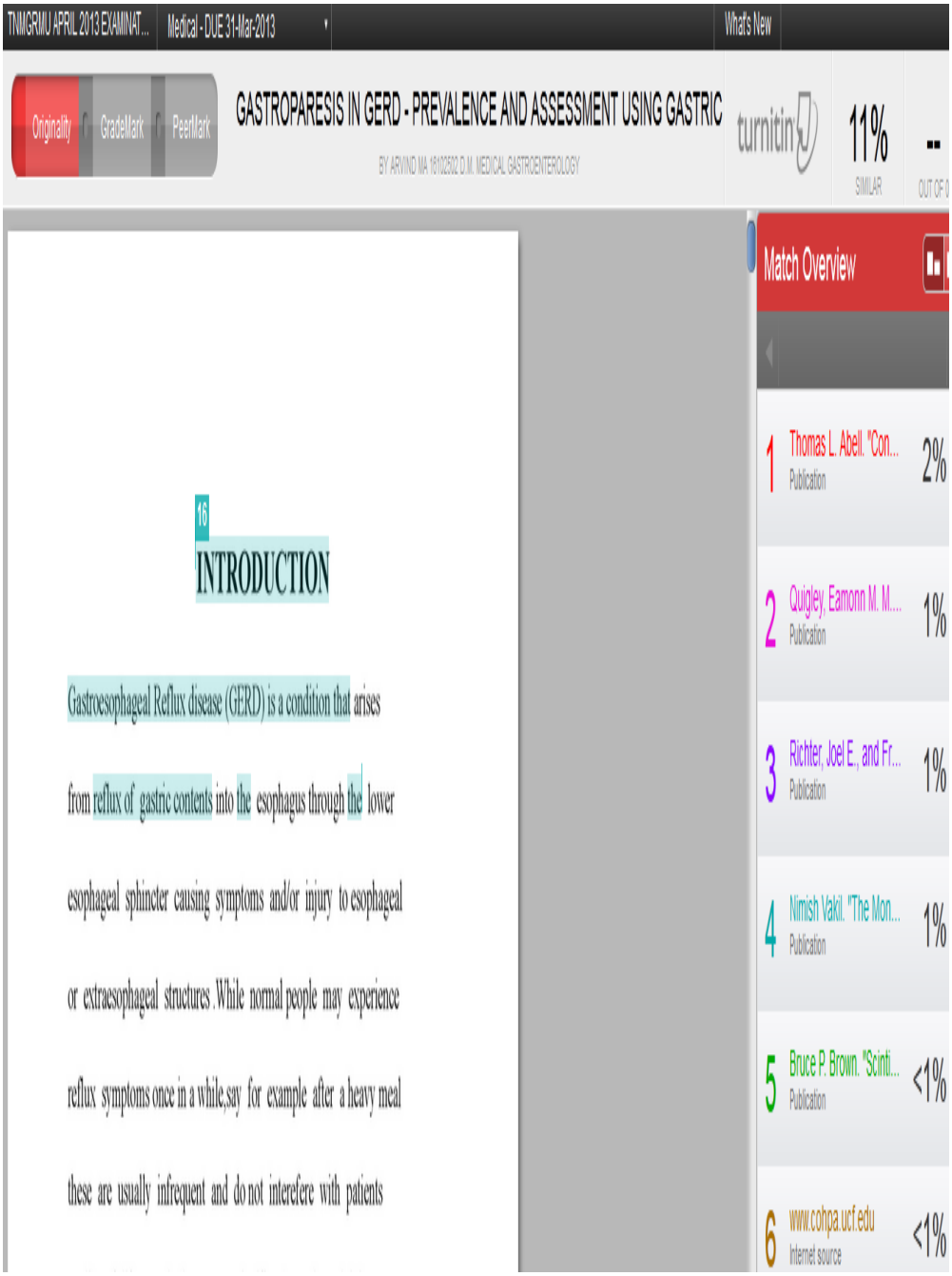
1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. K. Ramadevi MD Prof of Biochemistry, MMC, Ch-3	-- Member
3.	Prof. R. Nandhini MD Director, Inst. of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
6.	Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee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INTRODUCTION
Gastroesophageal Reflux disease (GERD) is a condition that arises from reflux of gastric contents into the esophagus through the lower esophageal sphincter causing symptoms and/or injury to esophageal or extraesophageal structures .While normal people may experience reflux symptoms once in a while,say for example after a heavy meal these are usually infrequent and do not interefere with patients

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Author	Arvind MA 16102502 D.M. Medical Gastroenterology
E-mail	janardhananarvind@gmail.com
Submission time	21-Mar-2013 04:32PM
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INTRODUCTION Gastroesophageal Reflux disease (GERD) is a condition that arises from reflux of gastric contents into the esophagus through the lower esophageal sphincter causing symptoms and/or injury to esophageal or extraesophageal structures .While normal people may experience reflux symptoms once in a while,say for example after a heavy meal these are usually infrequent and do not interefere with patients quality of life nor do they cause significant esophageal injury. Pathological reflux occurs when the esophageal defense mechanisms including acid clearance and mucosal resistance are overwhelmed by the injurious refluxate such as acid ,pepsin,bile,duodenal contents. Lower Esophageal...

MASTER CHART

Name	Age	Gender	SYM PERIOD	PPI NAÏVE	PPI REF	GERD-S	GERD +OGD	GERD +BIOPSY	GERD +24 HpH	OGD	GCSI	GP	% RET AT 4 H	GRADE OF GP	F RET %	A RET %
Karthik	40	M	1 YEAR	YES	-	YES	-	-	-	NORMAL	0	neg	0	-	-	-
Dhanasekar	39	M	2 YEARS	YES	-	YES	-	-	-	NORMAL	0	neg	0	-	-	-
Ganesh Kumar	23	M	6 MONTHS	YES	-	YES	YES	-	-	LA grA	0	neg	0	-	-	-
Padma	53	F	6 MONTHS	-	-	YES	-	-	-	PAN-G	0	neg	0	-	-	-
Murugan	26	M	6 MONTHS	YES	-	YES	-	-	-	ANTRAL-G	0	neg	0	-	-	-
Sumathy	44	F	8 MONTHS	YES	-	YES	-	-	-	NORMAL	0	neg	0	-	-	-
Solai	28	M	3 YEARS	-	-	YES	YES	-	-	LA grA	0	neg	0	-	-	-
Rajesh	27	M	1 YEAR	-	-	YES		YES	-	NODULE-DE	2	neg	0	-	-	-
Ruth	35	F	8 MONTHS	-	-	YES	-	-	YES	NORMAL	2	**pos**	12.6	Mild	5.6	7.04
Suresh	38	M	5 YEARS			YES				HH/CAMERON ULCER/ SCHATZKI B	0	neg	0	-	-	-
Maragadam	26	F	2 YEARS	YES		YES				NORMAL	2	neg	0	-	-	-
Padma 2	27	F	1 YEAR	YES		YES				NORMAL	0	**pos**	10.16	Mild	5.72	4.4
Murugan2	40	M	2 YEARS		YES	YES			YES	HH+	2	**pos**	11.6	Mild	7.9	3.7
Akilandam	35	F	3 YEARS			YES				NORMAL	0	neg	0	-	-	-
Stalin	35	M	6 MONTHS			YES				PAN-G	2	neg	0	-	-	-
Ananth	23	M	6 MONTHS	YES		YES				NORMAL	0	neg	0	-	-	-
Srinivasan	33	M	8 MONTHS	YES		YES				NORMAL	0	neg	0	-	-	-
Uma	27	F	1 YEAR			YES				NORMAL	0	neg	0	-	-	-
Gunasekar	47	M	1 YEAR			YES				HH+	0	neg	0	-	-	-
Kalavathy	32	F	1 YEAR	YES		YES				NORMAL	0	neg	0	-	-	-
Jayanthi	38	F	3 MONTHS	YES		YES				PAN-G	0	neg	0	-	-	-
Udayakumar	31	M	7 MONTHS	YES		YES				NORMAL	0	neg	0	-	-	-
Padma 3	50	F	10 YEARS			YES				NORMAL	0	neg	0	-	-	-
Vanaja	48	F	6 MONTHS	YES		YES				NORMAL	0	neg	0	-	-	-
Susila	38	F	6 YEARS			YES		YES		NODULE-DE	0	neg	0	-	-	-
Jalendra	26	F	1 YEAR	YES		YES				NORMAL	0	neg	0	-	-	-
Gopi	40	M	1 YEAR			YES				NORMAL	0	neg	0	-	-	-
Narmadha	19	F	8 MONTHS	YES		YES	YES			LA grC	0	neg	0	-	-	0

MASTER CHART ABBREVIATION

1.	LA	–	LOS ANGELES
2.	A	–	ANTRAL
3.	F	–	FUNDAL
4.	HH	–	HIATUS HERNIA
5.	DE	–	DISTAL ESOPHAGUS
6.	PAN-G	–	PAN GASTRITIS
7.	ANTRAL G	–	ANTRAL GASTRITIS
8.	RET	–	RETENTION
9.	SYM	-	SYMPTOMATIC
10.	REF	-	REFRACTORY